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PLASMA CELL DISORDERS

MATTHEW ULRICKSON, MD

OBJECTIVES

1. Understand the presentation of patients with plasma cell disorders
2. Appropriately select and interpret diagnostic tests in patients with possible plasma cell disorder
3. Describe the diagnostic criteria for multiple myeloma and MGUS
4. Describe indications for therapy and prognostic indicators for patients with multiple myeloma.
5. Understand risks of common treatment regimens in MM
6. Understand when to suspect amyloidosis in a patient with plasma cell disorder

CASE 1

- A 75-year-old man is admitted to the hospital with acute kidney injury. He was found down and was last seen well 36 hours prior.
- Laboratory studies are as follow:
  - CBC 6.5>17<547
  - Na 155 Cr 2.5 (baseline 1.0 when checked 3 months ago) Ca 10.2 (8.6-10.3 mg/dL)

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  - An SPEP was sent and identifies an M spike of 0.2g/dL. Immunofixation confirms IgG kappa
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    - A. Bone marrow biopsy
    - B. Free light chain assay
    - C. Skeletal survey
    - D. 24-hour urine
    - E. No further testing

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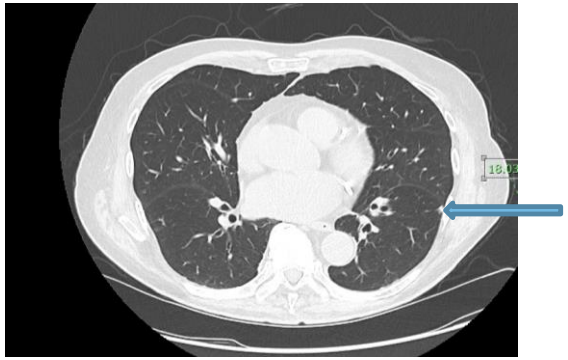
MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE (MGUS)

- M spike <3g/dL and Bone marrow <10% plasma cells and no symptoms (CRAB criteria)
- 1% risk per year to transform to myeloma
- Incidence by age:
  - 3.2% if >50yo
  - 8.9% if >80yo
- If there is no/low pre-clinical suspicion consider an 'incidental' identification of monoclonal protein
  - Important to follow, but no immediate evaluation may be needed (like a lung nodule)



Kyle, RA et al. Leukemia 2010;24:1121-1127

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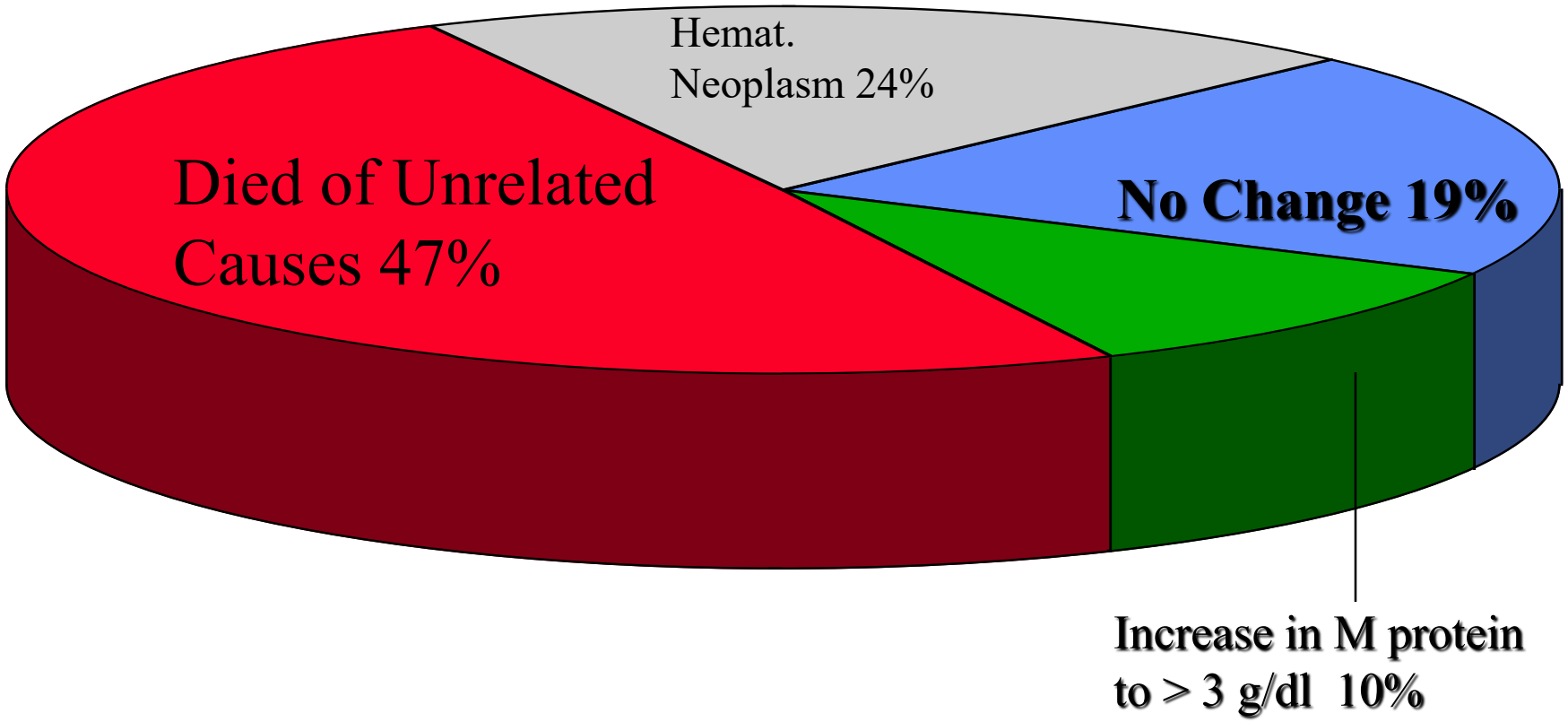
FOLLOW-UP OF MGUS

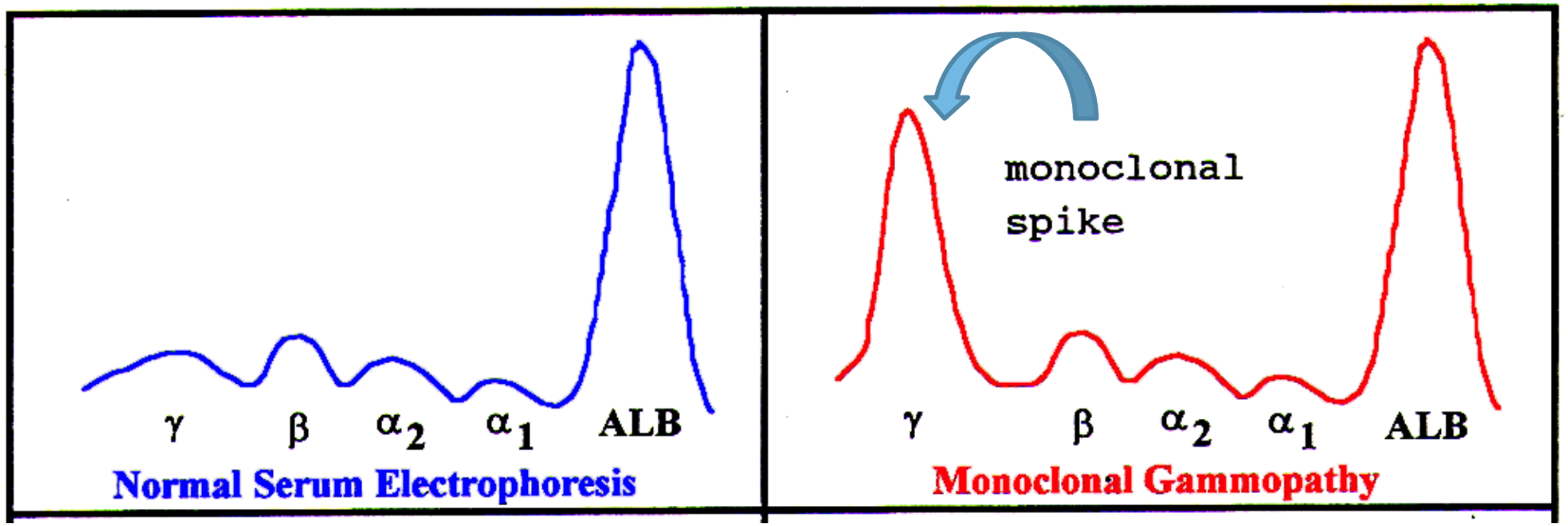
241 PATIENTS FOLLOWED FOR MEDIAN OF 22 YR



R. Kyle, Mayo Clinic, in Hematology (Hoffman, ed.), 1995, p. 1354)

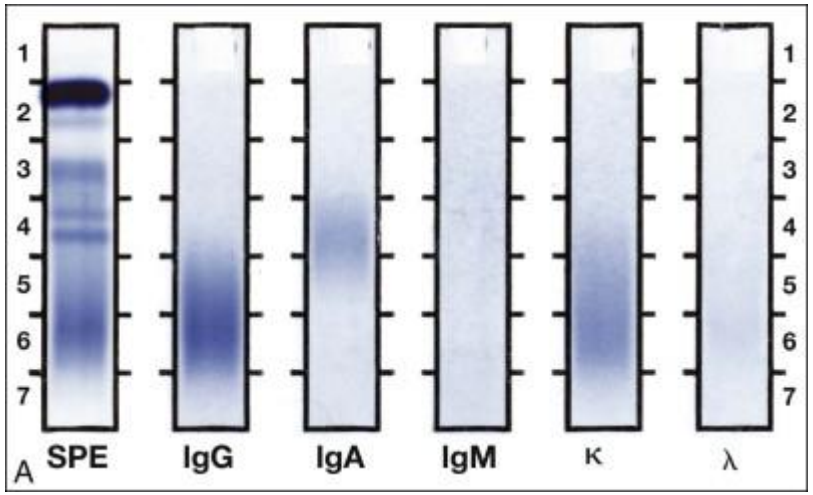
SPEP AND IMMUNOFIXATION

SPEP
Serum Protein Electropheresis

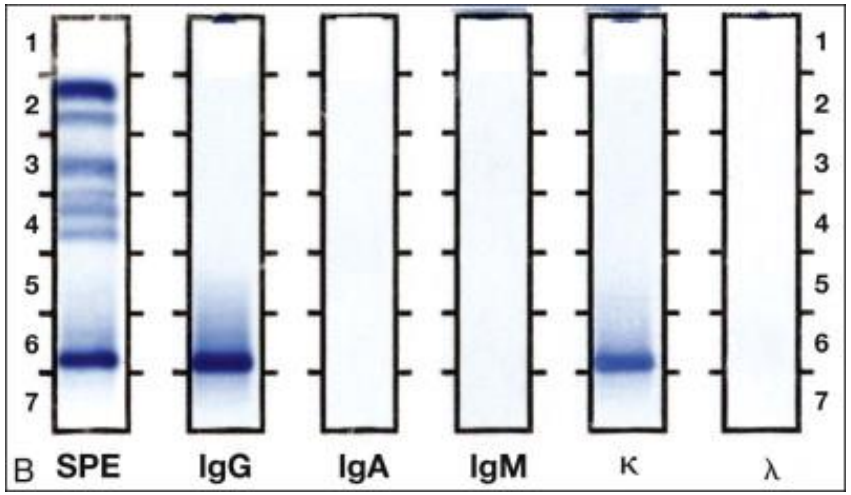


How much

Immunofixation



Normal Immunofixation



Monoclonal IgG kappa

What kind

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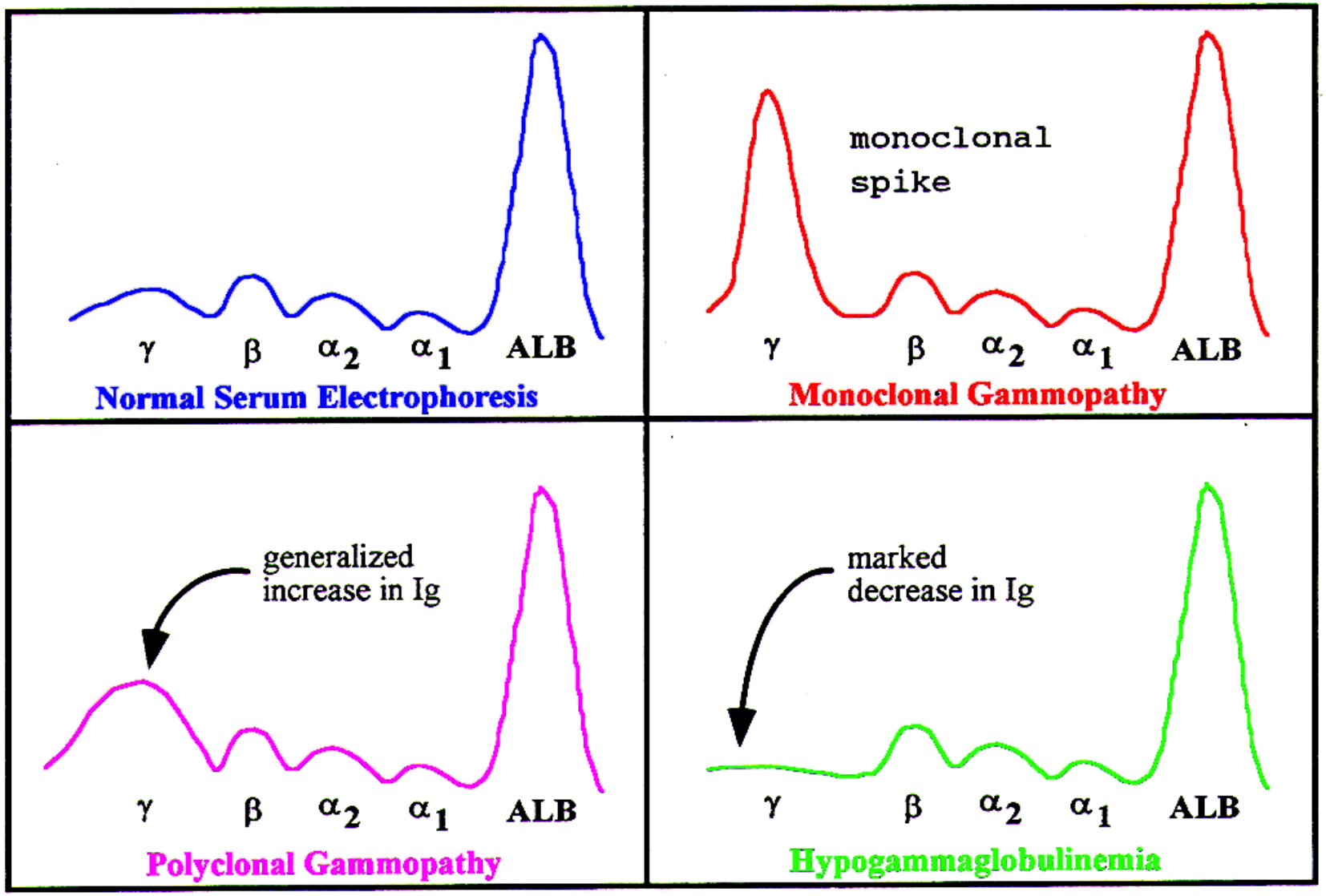
McPherson and Pincus, Eds. *Henry's Clinical Diagnosis and Management by Laboratory Methods* 2011

SPEP PATTERNS



Suggests infection or inflammation

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CASE 2

- A 55-year-old woman presents with fatigue x 3 weeks
  - CBC 5.7>9.2<201
  - Cr 4.8 Ca 11.0 (8.3-10.4mg/dL)
  - M spike negative for paraprotein

  - What do you recommend as a next diagnostic test for this patient?
    - A. Bone marrow biopsy
    - B. Cryoglobulins
    - C. Renal biopsy
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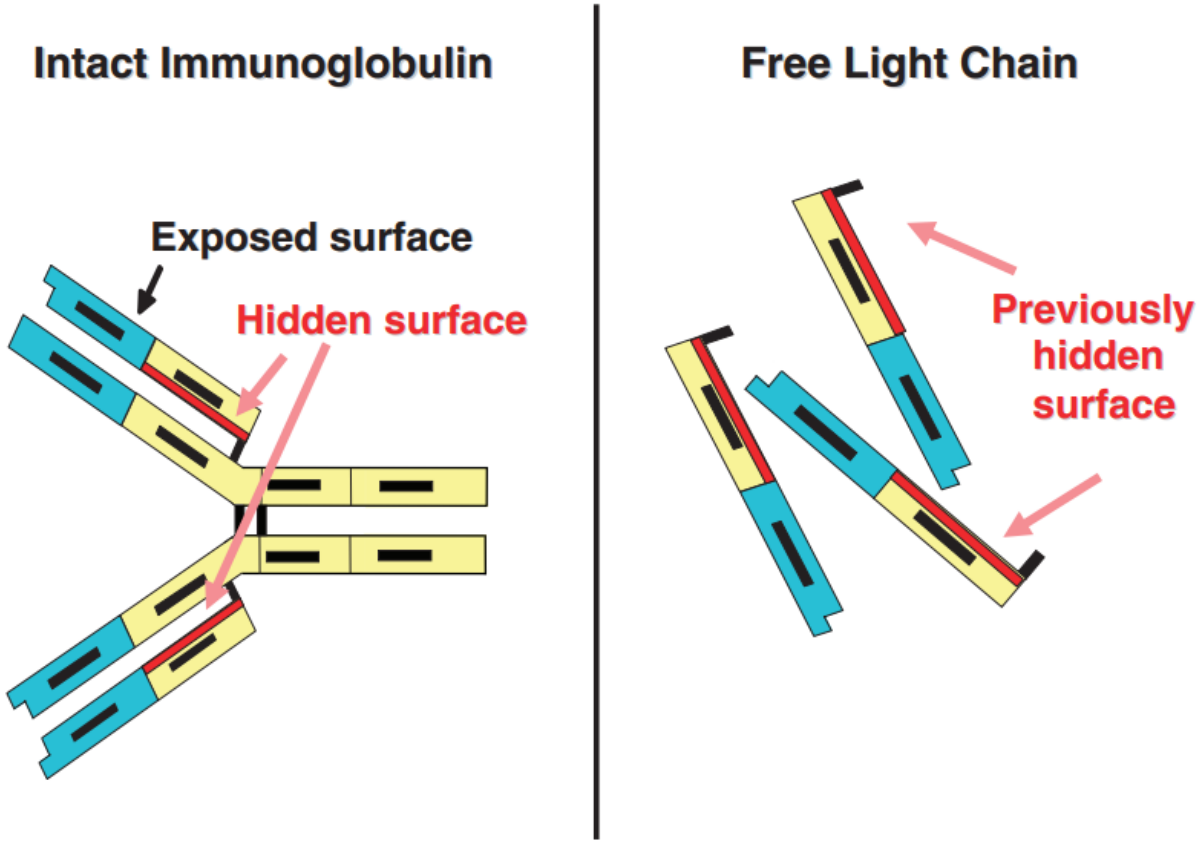
FREE LIGHT CHAINS

- Free light chain assay does not quantitate light chain if it is bound to heavy chain, only when detached.
- Two types of light chain: kappa, lambda
- Usual ratio is 0.2-1.65 (κ/λ)
- Serum half life 2-4hrs, renally cleared
  - Normal plasma cell production is 0.5-1g/day while the kidneys can clear/metabolize 10-30g/day
  - Decrease in GFR will lead to higher FLC serum levels (but ratio should remain preserved)



Dispenzieri et al. Leukemia 2009. 23: 215-224

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CASE 2

- This patient has no clear reason for acute kidney injury
- ~5% of myeloma clones do not make complete paraprotein – check light chains (and SPEP/IFix) before excluding plasma cell disorder
- The **ratio** of kappa to lambda (or vice versa) will help diagnose a clonal disorder instead of the absolute quantity alone

CASE 3

- A 65-year-old man with a history of well-controlled hypertension is referred for evaluation after an elevated serum protein concentration was found during an annual physical examination. He reports no bone pain, weight loss, or fatigue. Physical examination shows no abnormalities.

Laboratory Value	Current	Reference Range
Hemoglobin	13.8 g/dL	13-17.3 g/dL
Mean corpuscular volume (MCV)	87 fL	80-100 fL
Serum		
Albumin	4.1 g/dL	4.03-5.43 g/dL
Calcium (Ca^{2+})	9.1 mg/dL	8.6-10.3 mg/dL
Creatinine	0.9 mg/dL	0.7-1.3 mg/dL
Lactate dehydrogenase	180 U/L	100-240 U/L

Serum protein electrophoresis shows an IgG lambda M-spike of 2.6 g/dL
Kappa 1.10 mg/dL, Lambda 32.80 mg/dL, and ratio of 0.03.
Bone marrow shows 33% lambda-restricted plasma cells, and FISH shows no cytogenetic abnormalities
Whole-body MRI does not show any lytic lesions

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B. Smoldering myeloma
C. Multiple myeloma
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SMOLDERING MYELOMA

MGUS	Smoldering MM	Active MM
<3 g M spike <10% PC*	≥ 3 g M spike OR ≥ 10% PC*	≥ 10% PC* M spike +
AND No anemia or bone lesions, normal calcium and kidney function		AND Anemia, bone lesions, high calcium, or abnormal kidney function

*In bone marrow.

Kyle RA, et al. *N Engl J Med*. 2002;346(8):564-569.

Or BM PC >60%, Light chain ratio >100 or >1 bony lesion on MRI or PET

Smoldering Myeloma - Usually no treatment recommended, but some patients may benefit in high-risk subsets

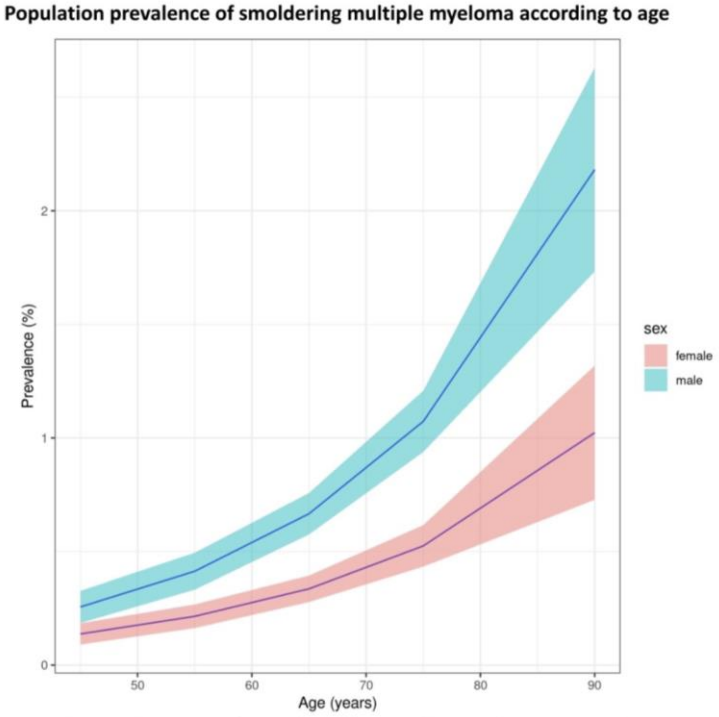


Figure: Estimated prevalence of smoldering multiple myeloma in men and

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

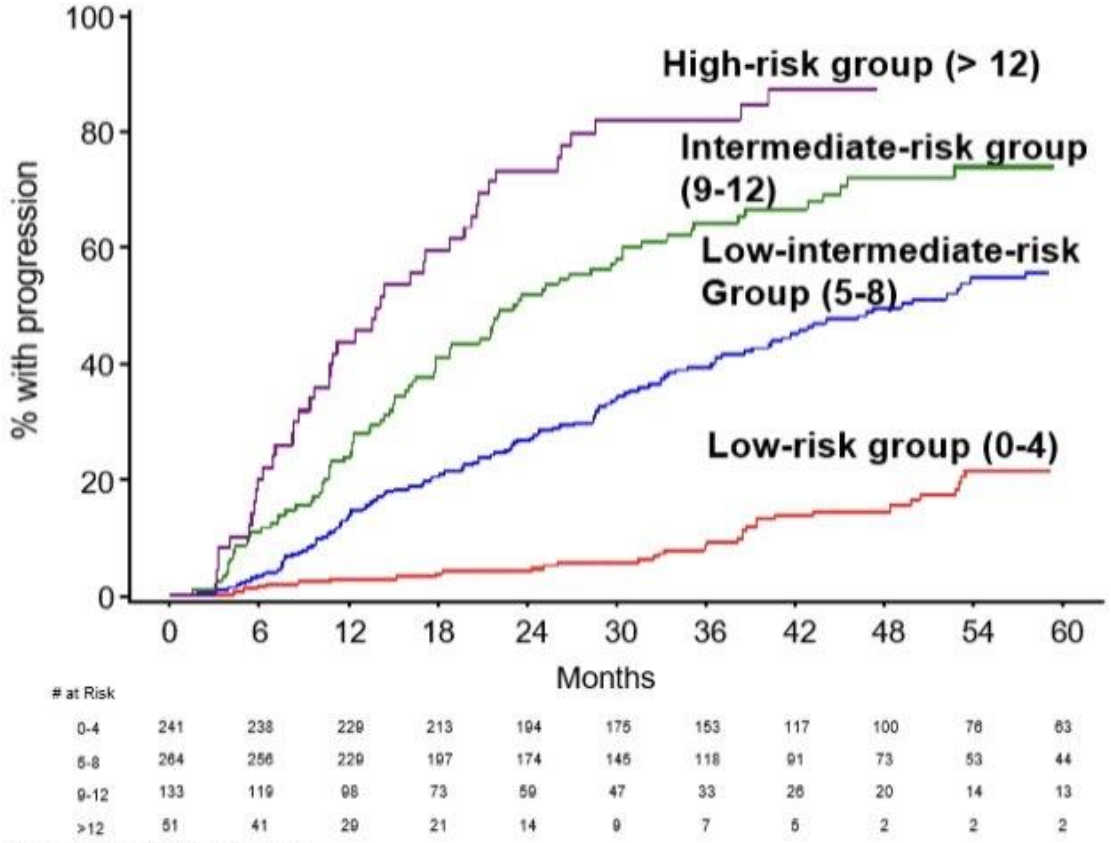
Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

IMWG: Risk Score to Predict Progression Risk at 2 Years

A more precise and individualized scoring tool to classify individuals by risk of progression using the entire spectrum of values for each patient



MyeRisk Calculator

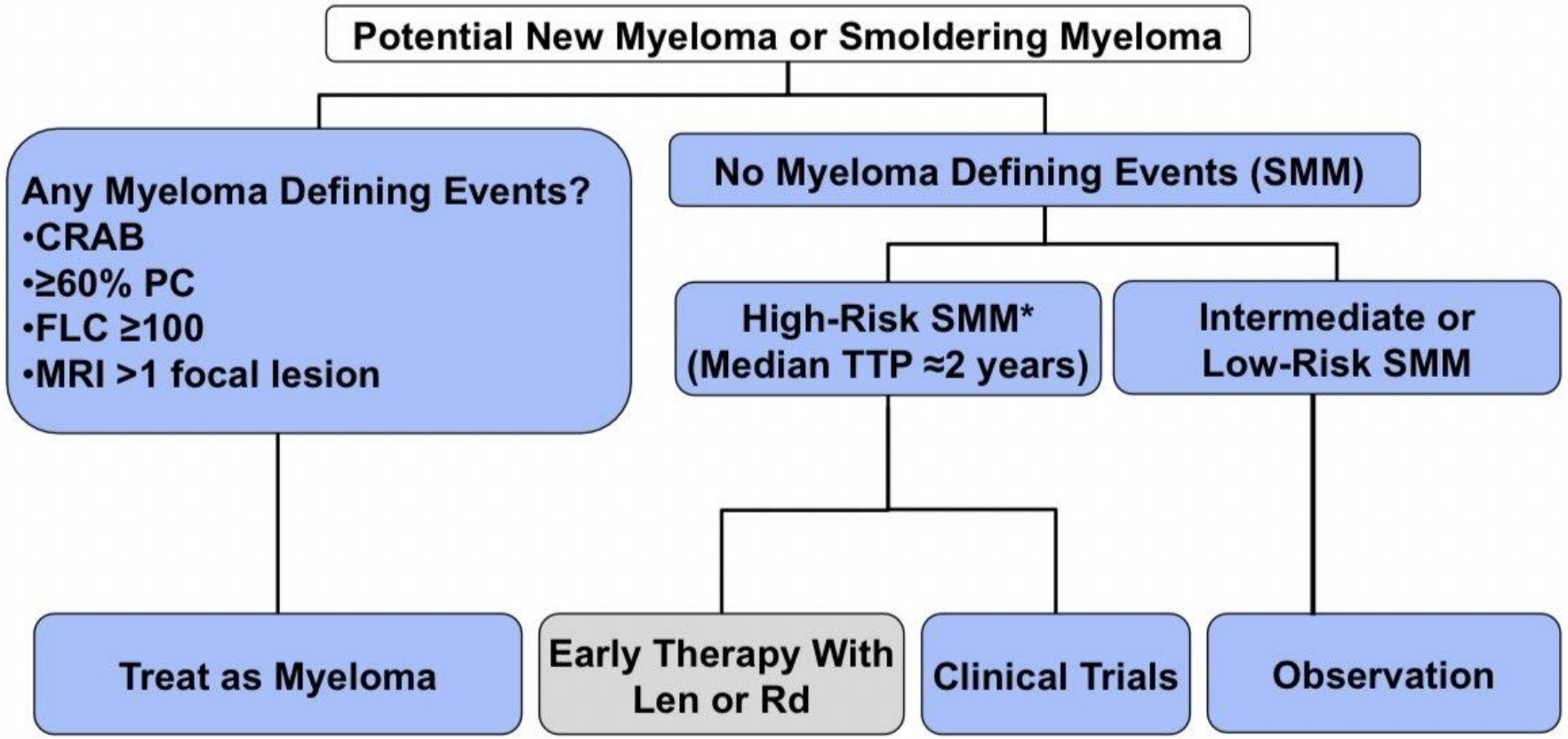
Risk Factor	Coefficient	P-value	Score
FLC Ratio			
0-10 (reference)	-	-	0
> 10-25	0.69	0.014	2
> 25-40	0.96	0.004	3
> 40	1.56	<0.0001	5
M protein (g/dL)			
0-1.5 (reference)	-	-	0
> 1.5-3	0.95	0.0002	3
> 3	1.30	<0.0001	4
BMPC%			
0-15 (reference)	-	-	0
> 15-20	0.57	0.04	2
> 20-30	1.01	0.0002	3
> 30-40	1.57	<0.0001	5
> 40	2.00	<0.0001	6
FiSH abnormality	0.83	<0.0001	2

Total Risk Score	2-Year Progression, n (%)
0-4	3.7%
5-8	25.4%
9-12	48.9%
> 12	72.6%

San Miguel. ASCO 2019. Abstract 8000. Mateos et al BCJ 2020

Myeloma 2022: Treatment of Smoldering Myeloma

(An approach)



High Risk SMM defined as any 2 of 3 factors (Mayo 2018 criteria):
BM plasma cells >20%, M spike >2 gm/dl, FLC ratio >20

CASE 4

- An 81-year-old woman is referred for evaluation because of suspected multiple myeloma. She uses a walker at home but is in a wheelchair today because of pain in the lumbar spine. Laboratory studies show:

Laboratory Value	Current	Reference Range
Hemoglobin	9.9 g/dL	12-16 g/dL
Serum		
Calcium (Ca^{2+})	10.3 mg/dL	8.6-10.3 mg/dL
Creatinine	1.2 mg/dL	0.7-1.3 mg/dL

A bone marrow biopsy shows hypercellularity with involvement by 22% kappa-restricted plasma cells. Flow cytometry analysis shows 4.4% plasma cells. FISH shows t(11;14). MRI shows multiple lytic lesions in the spine and pelvis.

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(flow cytometry usually underestimates plasma cells)

MYELOMA: WORK-UP

1. CBC/Differential (confirm no circulating plasma cells)
2. Chemistries (esp. Ca, creatinine, total protein)
3. Bone marrow aspirate/biopsy with FISH/cytogenetics
4. Serum protein electrophoresis with immunofixation
5. Serum Free light chains (can consider 24 hr urine for quantitative Bence-Jones proteins (with electrophoresis) but SPEP/FLC identify 99.5% of pts)
6. ß2 microglobulin
7. Skeletal bone survey (not bone scan) and PET or MRI

DIAGNOSIS

- Clonal marrow plasma cells ≥10%
- Presence of serum and/or urinary monoclonal protein (except if non-secretory)
- Evidence of end organ damage attributed to plasma cell disorder
  - Serum Ca >11.5mg/dL
  - Serum Cr >2mg/dL
  - Hb <10g
  - Bone lesions: lytic lesions, pathologic fractures, osteopenia
- Or – high risk for symptoms: 60% PC in marrow, FLC ratio >100 or >1 bone lesion on advanced imaging

C – calcium
R – renal
A – anemia
B - bone

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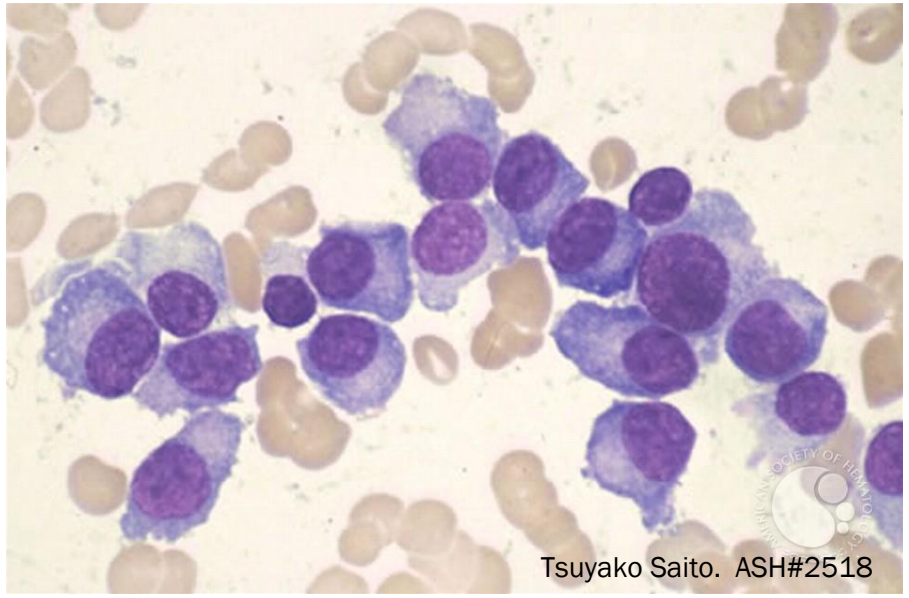
SYMPTOMS AT DIAGNOSIS

- Bone Pain 58%
- Fatigue 32%
- Weight loss 24%
- Paresthesias 5%
- ~20% asymptomatic or only mild symptoms



Tsuyako Saito. ASH#2518

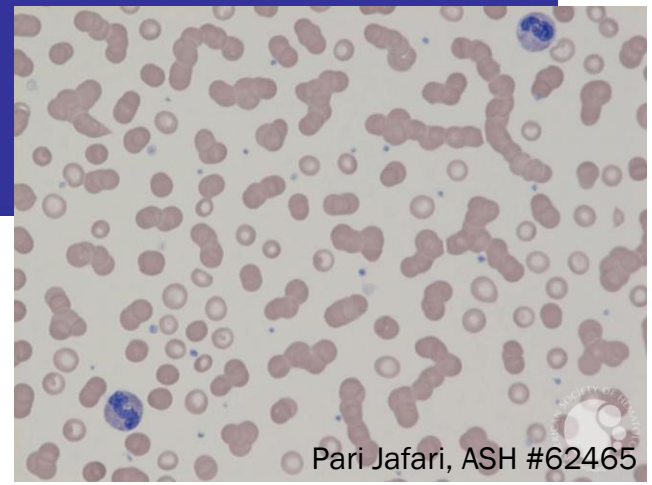
Kyle RA, et al. *Mayo Clin Proc*. 2003;78(1):21-33.
Weber DM, et al. *Br J Haematol*. 1997;97:810-814.

Clinical Features at Presentation

- Monoclonal (M) protein (93%)
- Lytic bone lesions (67%)
- Increased plasma cells in the bone marrow (96%)
- Anemia (normochromic normocytic; 73%)
- Hypercalcemia (corrected calcium >11 mg/dL) (13%)
- Renal failure, serum creatinine >2.0 mg/dL (19%)
- Infection

From hypogammaglobulinemia

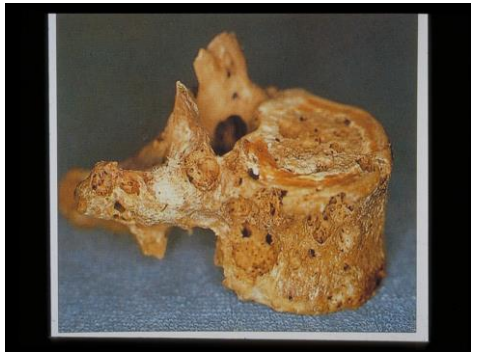
Kyle RA, et al. *Mayo Clin Proc*. 2003;78(1):21-33.
Kyle RA, Rajkumar SV. *N Engl J Med*. 2004;351:1860-1873.



Pari Jafari, ASH #62465

MM: LYTIC BONE LESIONS

Solitary Plasmacytoma = myeloma without bone marrow/blood disease



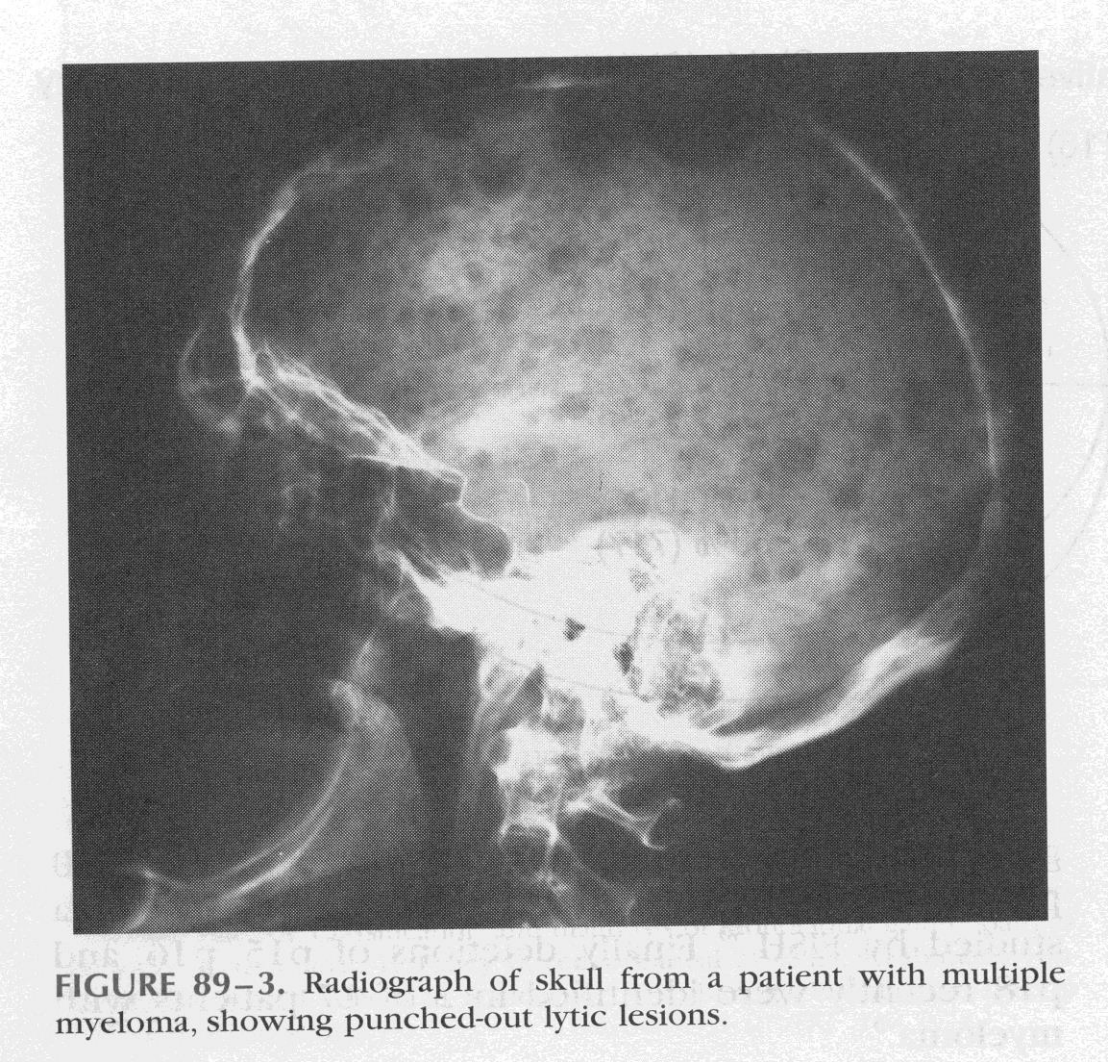
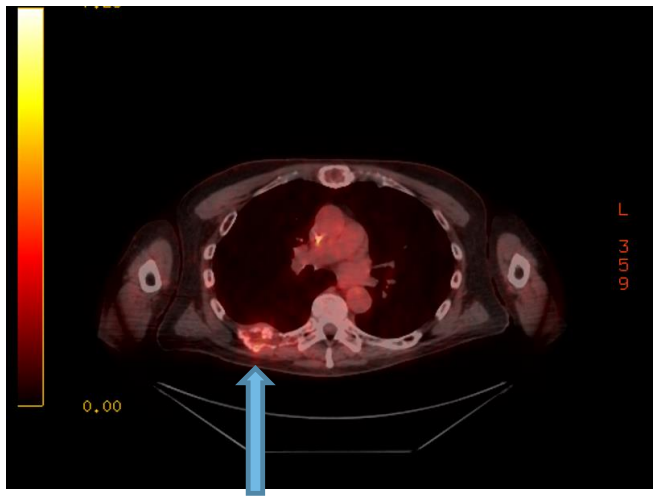
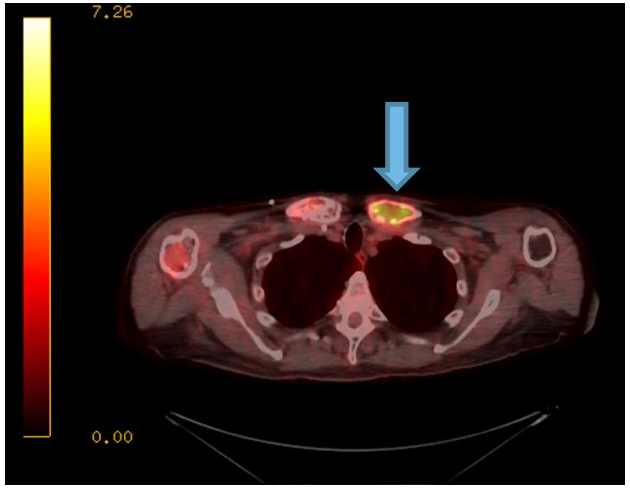


FIGURE 89–3. Radiograph of skull from a patient with multiple myeloma, showing punched-out lytic lesions.

- Skeletal survey still helpful, but not adequate for dx
- PET or whole-body MRI even more sensitive for bony lesions

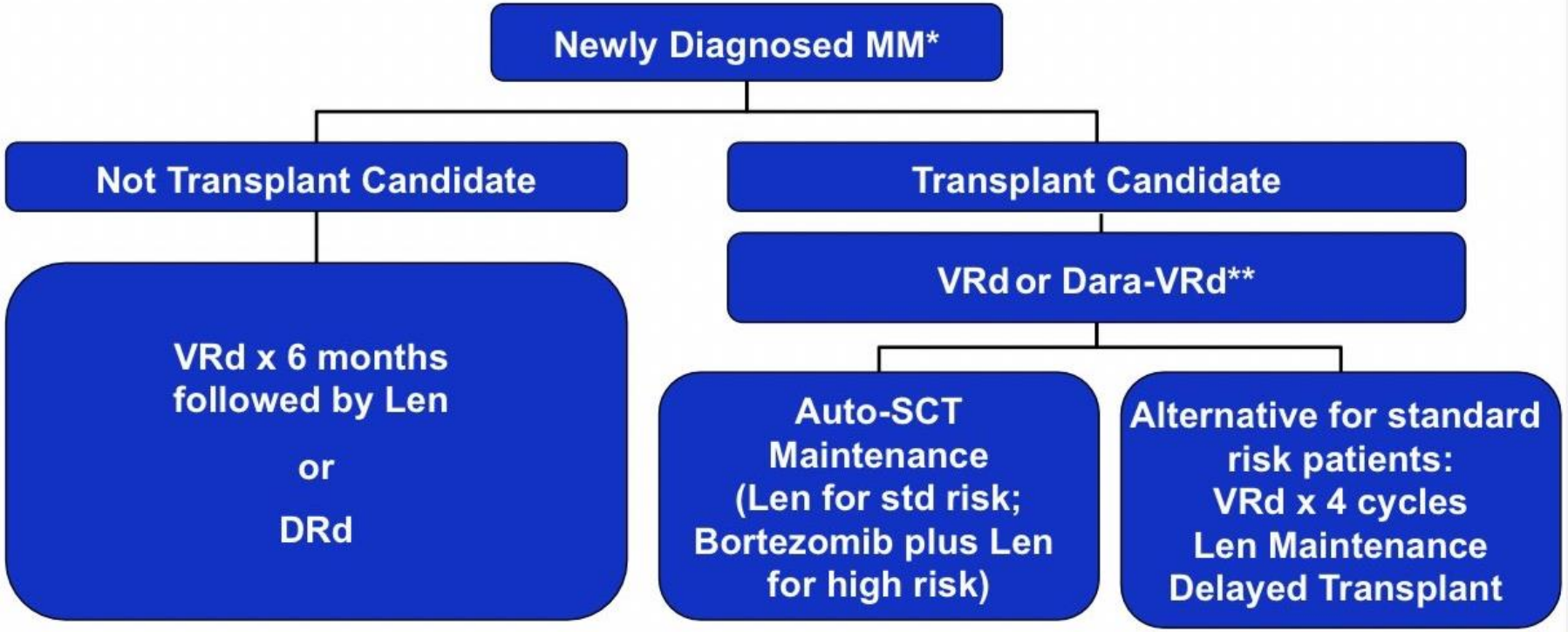




Bisphosphonates (zoledronic acid) help reduce fracture risk in myeloma – q3 month dosing in pts with active disease

Myeloma 2022: Frontline Treatment

An approach



*Based on CALGB 100104, S0777, IFM-2009, CTN 0702, HOVON, MAIA, CASSIOPEIA
**VRd preferred in standard risk, and Dara-VRd preferred in high risk patients

HIGH-DOSE THERAPY

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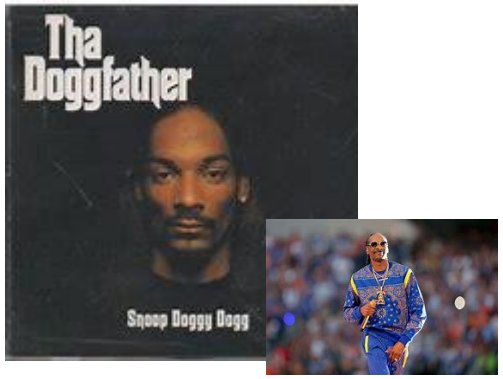
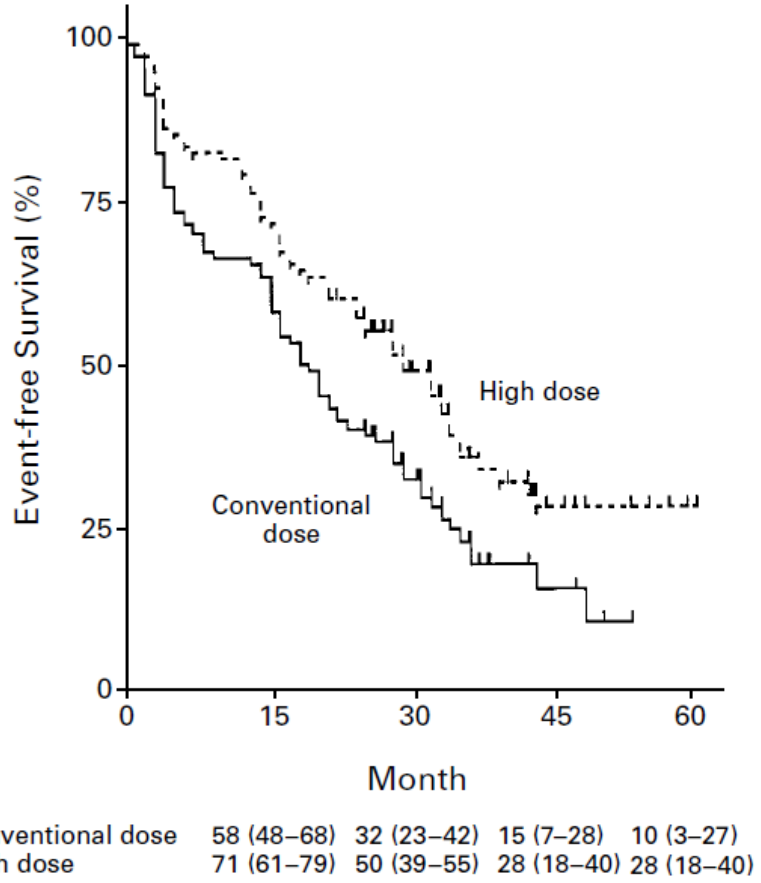
A PROSPECTIVE, RANDOMIZED TRIAL OF AUTOLOGOUS BONE MARROW TRANSPLANTATION AND CHEMOTHERAPY IN MULTIPLE MYELOMA

MICHEL ATTAL, M.D., JEAN-LUC HAROUSSEAU, M.D., ANNE-MARIE STOPPA, M.D., JEAN-JACQUES SOTTO, M.D., JEAN-GABRIEL FUZIBET, M.D., JEAN-FRANÇOIS ROSSI, M.D., PHILIPPE CASASSUS, M.D., HERVÉ MAISONNEUVE, M.D., THIERRY FACON, M.D., NORBERT IFRAH, M.D., CATHERINE PAYEN, M.D., AND RÉGIS BATAILLE, M.D., FOR THE INTERGROUPE FRANÇAIS DU MYÉLOME*

- 1996 – randomized trial

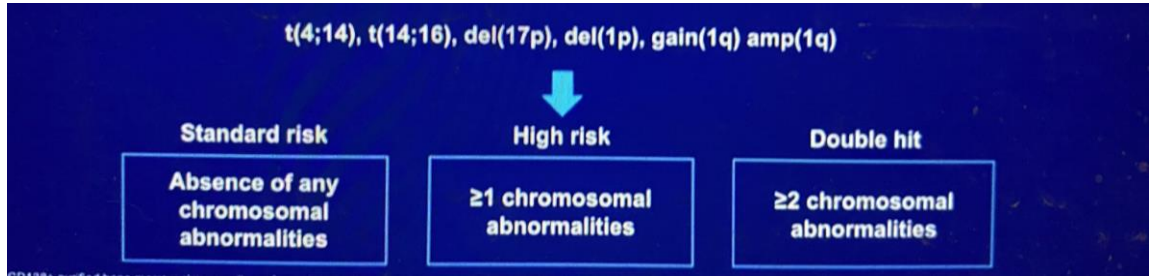




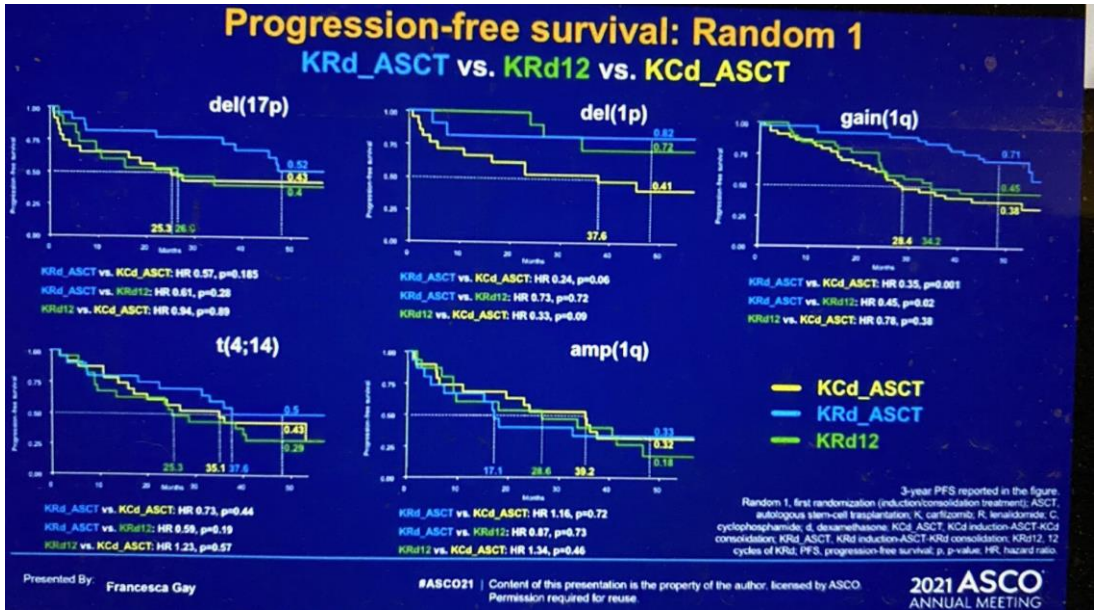
Conventional dose	58 (48–68)	32 (23–42)	15 (7–28)	10 (3–27)
High dose	71 (61–79)	50 (39–55)	28 (18–40)	28 (18–40)

KB –drafted #13 by the Charlotte Hornets

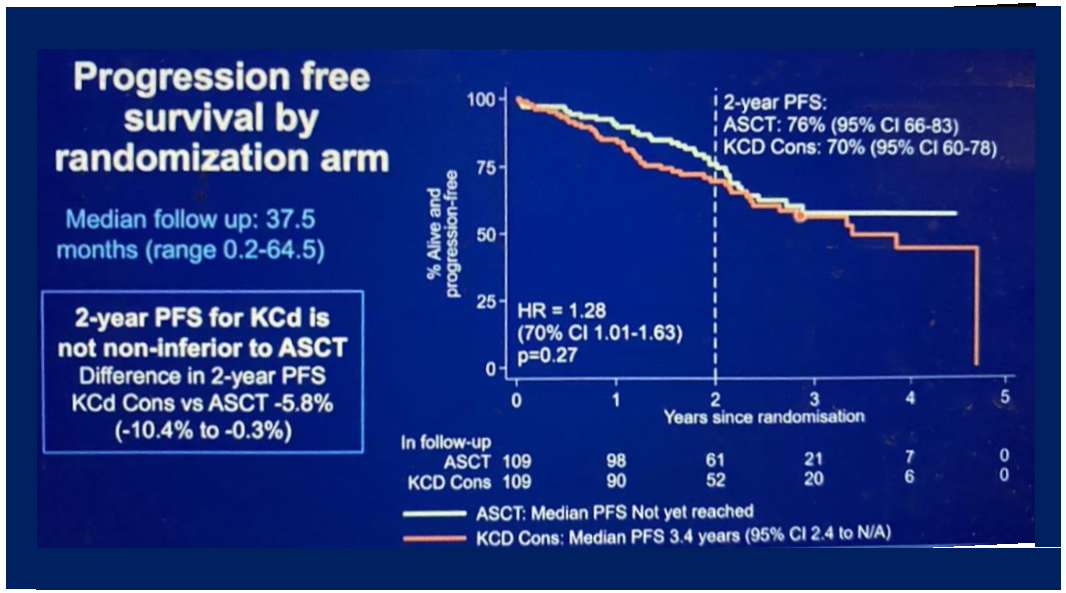
AUTOLOGOUS TRANSPLANT IN CR1 MYELOMA – ASCO 2021



- FORTE Dr. Gay et al
  - High Risk and Standard Risk seemed to benefit from SCT



- CARDAMON Dr Yong et al
  - KCd consolidation not non-inferior to ASCT



Reports of my death have been greatly exaggerated…

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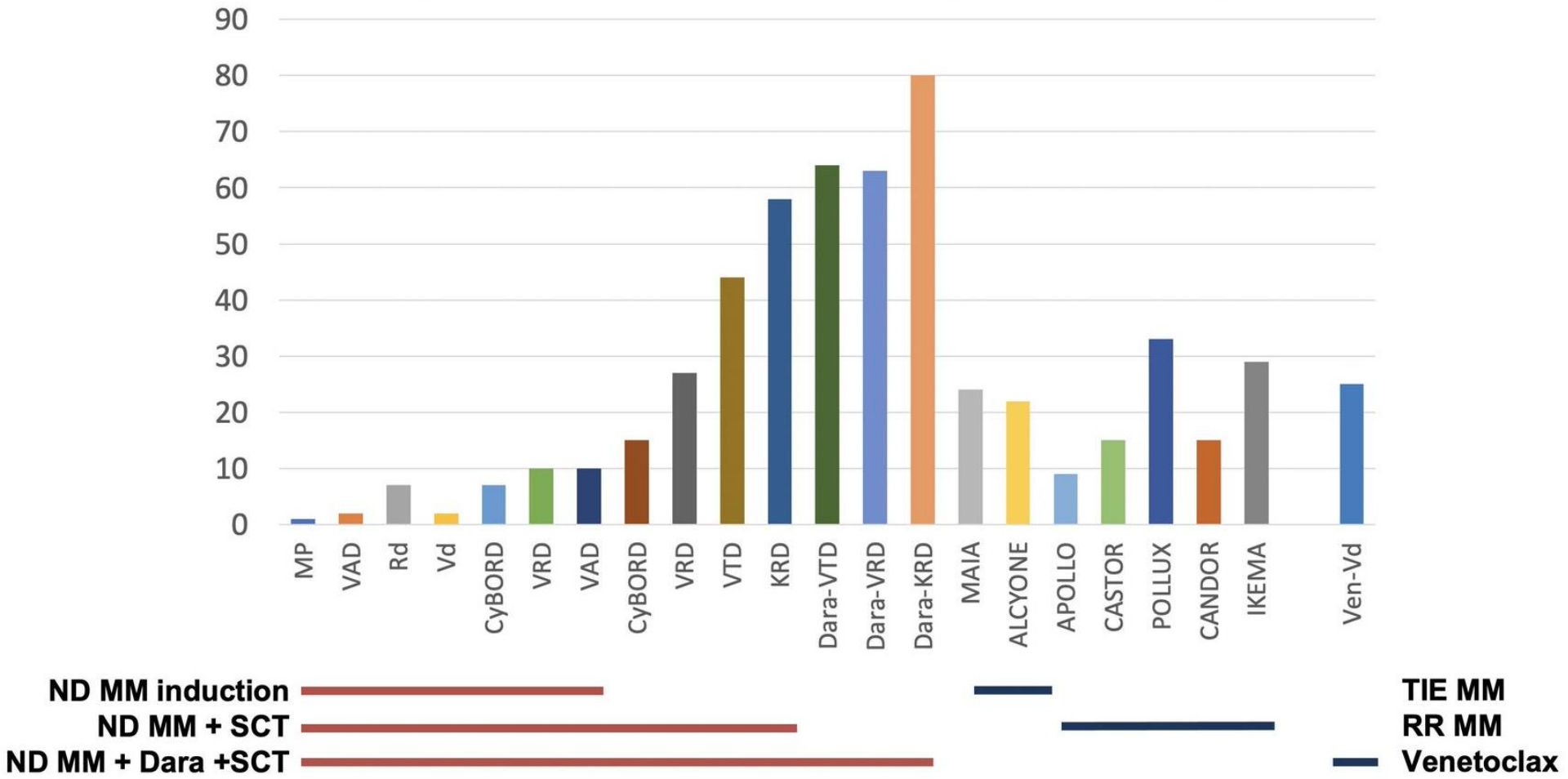
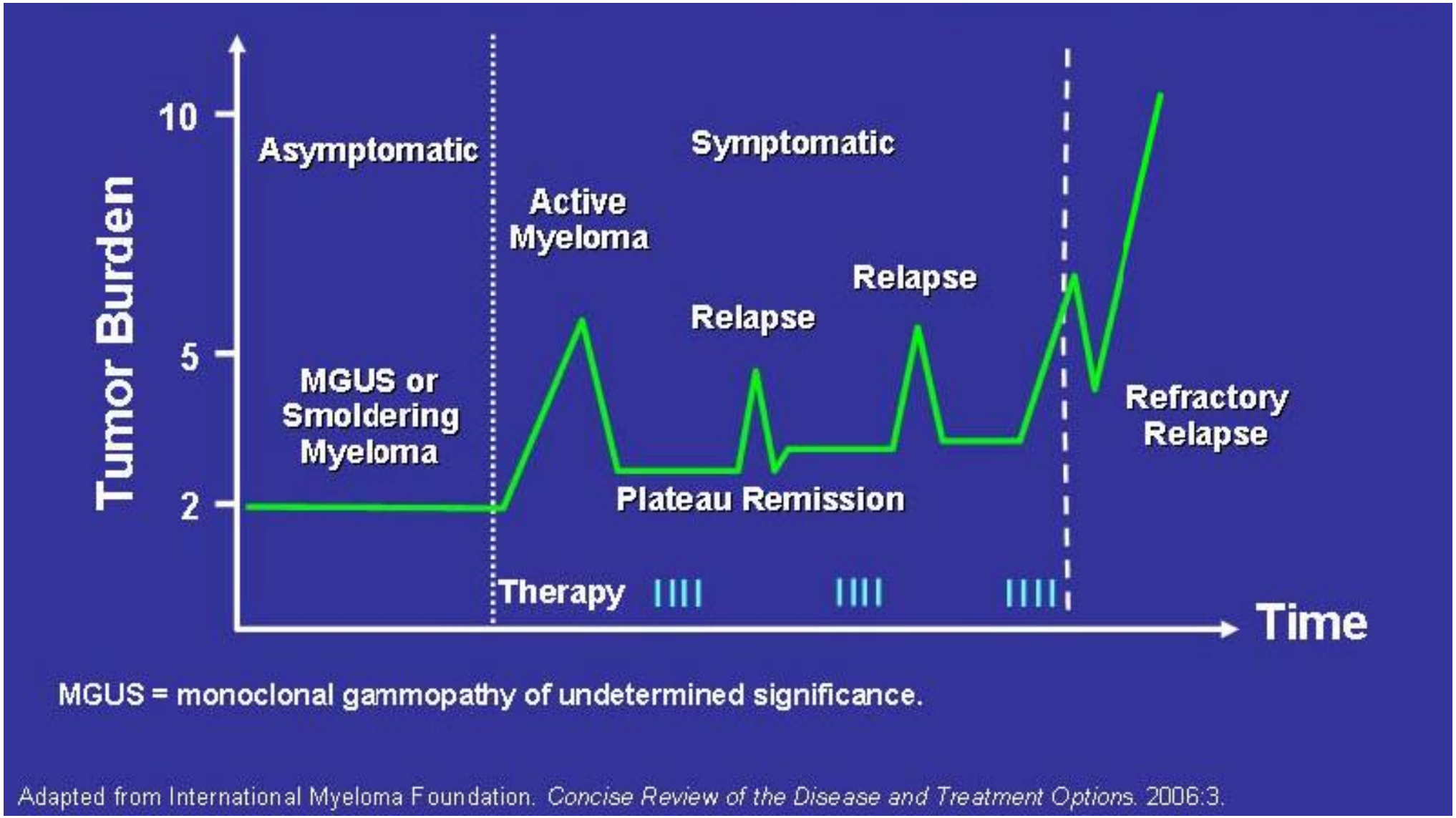
The Progression of MRD (10^{-5}) Negativity



@rfonsi1, fonseca.rafael@mayo.edu

COURSE OF MYELOMA



Adapted from International Myeloma Foundation. *Concise Review of the Disease and Treatment Options.* 2006:3.

CASE 4 CONTINUES

- An 81-year-old woman is referred for evaluation because of suspected multiple myeloma. She uses a walker at home but is in a wheelchair today because of pain in the lumbar spine. Laboratory studies show:

Laboratory Value	Current	Reference Range
Hemoglobin	9.9 g/dL	12-16 g/dL
Serum		
Calcium (Ca^{2+})	10.3 mg/dL	8.6-10.3 mg/dL
Creatinine	1.2 mg/dL	0.7-1.3 mg/dL

A bone marrow biopsy shows hypercellularity with involvement by 22% kappa-restricted plasma cells. Flow cytometry analysis shows 4.4% plasma cells. FISH shows t(11;14). MRI shows multiple lytic lesions in the spine and pelvis.

She is started on daratumumab, lenalidomide, and dexamethasone for initial treatment.

Which of the following medications do you recommend to decrease complications of therapy?

A. Aspirin
B. Levetiracetam
C. Levothyroxine
D. Posaconazole
E. Ondansetron

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IMMUNOMODULATORS (IMIDS)

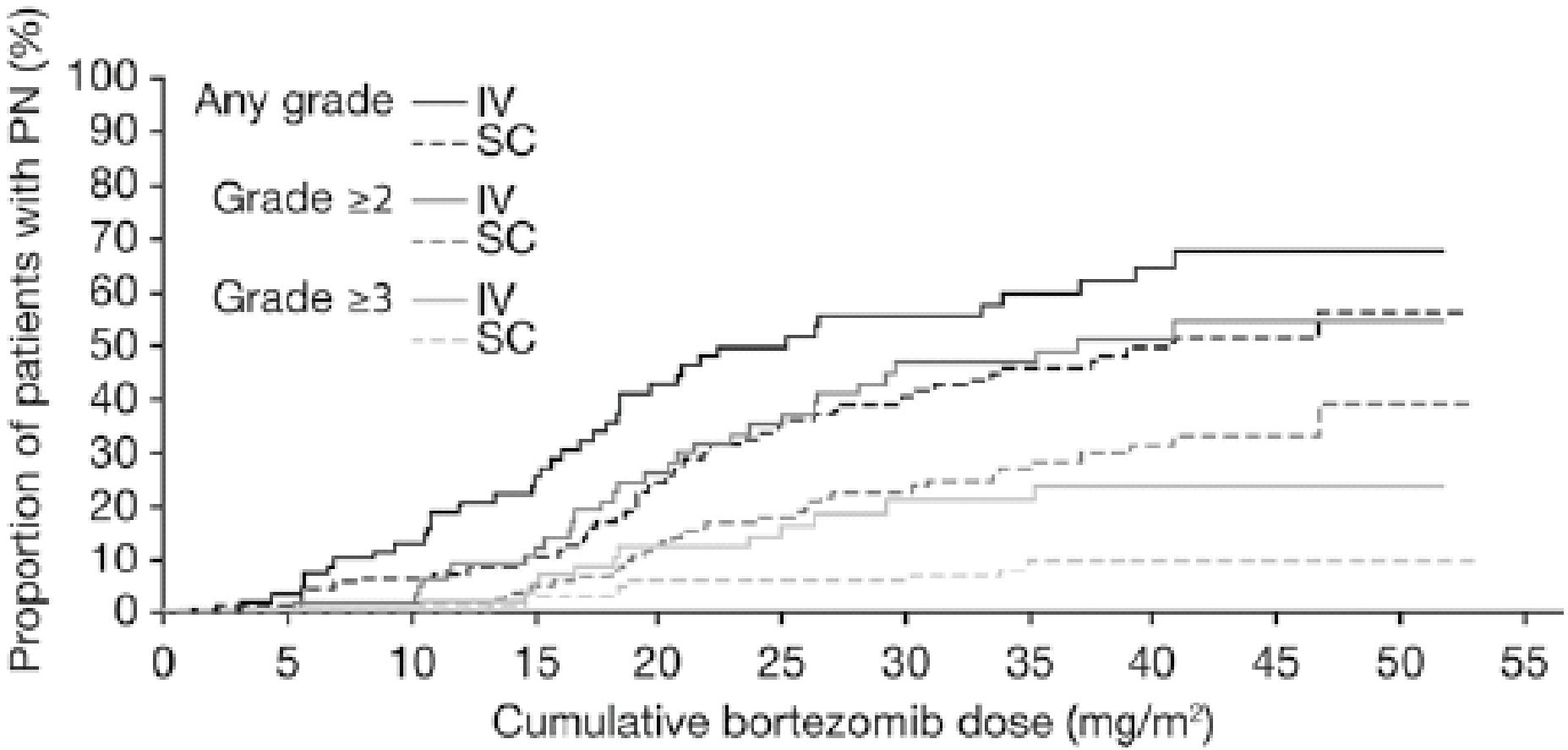
- Lenalidomide, pomalidomide, thalidomide
- Side effects
  - Cytopenias (usually mild)
  - Birth Defects, includes phocomelia (contraception is critical in patients of child-bearing age)
  - Thrombosis (especially combined with corticosteroids)
  - Neuropathy (Thalidomide >> Lenalidomide)

Table 2 Recommendations for Thromboprophylaxis in Multiple Myeloma Patients Treated With Thalidomide or Lenalidomide

- ≤ 1 VTE risk factor: aspirin (81–325 mg once daily)
- ≥ 2 risk factors: LMWH (equivalent to enoxaparin, 40 mg/d)
- LMWH is also recommended for all patients receiving thalidomide or lenalidomide plus high-dose dexamethasone or doxorubicin
- Barring contraindications in the front-line setting, treatment strategies using dexamethasone should use low-dose dexamethasone and include aspirin prophylaxis
- Full-dose warfarin (target INR 2–3) is an alternative to LMWH, although limited data exist to support this strategy
- Anticoagulant prophylaxis is recommended in patients with relapsed disease and a high risk for VTE
- It may be reasonable to deliver anticoagulant prophylaxis for 4 to 6 months; longer treatment periods may be considered in the presence of additional risk factors
- If VTE occurs in patients receiving thalidomide or lenalidomide, it is reasonable to briefly discontinue therapy and resume once proper anticoagulation has been established

Abbreviations: INR, International Normalized Ratio; LMWH, low molecular weight heparin; VTE, venous thromboembolism.
Data from Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414–423.

IV VS SC BORTEZOMIB (PROTEASOME INHIBITOR) AND NEUROPATHY



Arnulf et al. Haematologica 2012. Epub

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CASE 4 CONTINUES

- 81-year-old woman is seen two months into treatment for her multiple myeloma with daratumumab, lenalidomide, and dexamethasone. Her bone pain is markedly improved and she is walking again. However, today she reports some dyspnea that is increased over the past few weeks. Laboratory studies show:

Laboratory Value	Current	Reference Range
Hemoglobin	7.1 g/dL	12-16 g/dL
Serum		
Calcium (Ca^{2+})	9.3 mg/dL	8.6-10.3 mg/dL
Creatinine	1.0 mg/dL	0.7-1.3 mg/dL

You request 1u RBC for transfusion. The blood bank calls you to explain that there are no cross-match compatible units.

Which of the following antigens on RBCs is the cause of the inability to crossmatch blood in this patient? medications?

A. CD20
B. CD3
C. CD38
D. Kell
E. Rh

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C. CD38
D. Kell
E. Rh

Daratumumab targets CD38 on myeloma cells. CD38 is also weakly expressed on RBCs and can prevent crossmatch. Sending a blood bank sample before first dose can assist with transfusion support.
(DTT treatment of RBC and genotype are alternatives)

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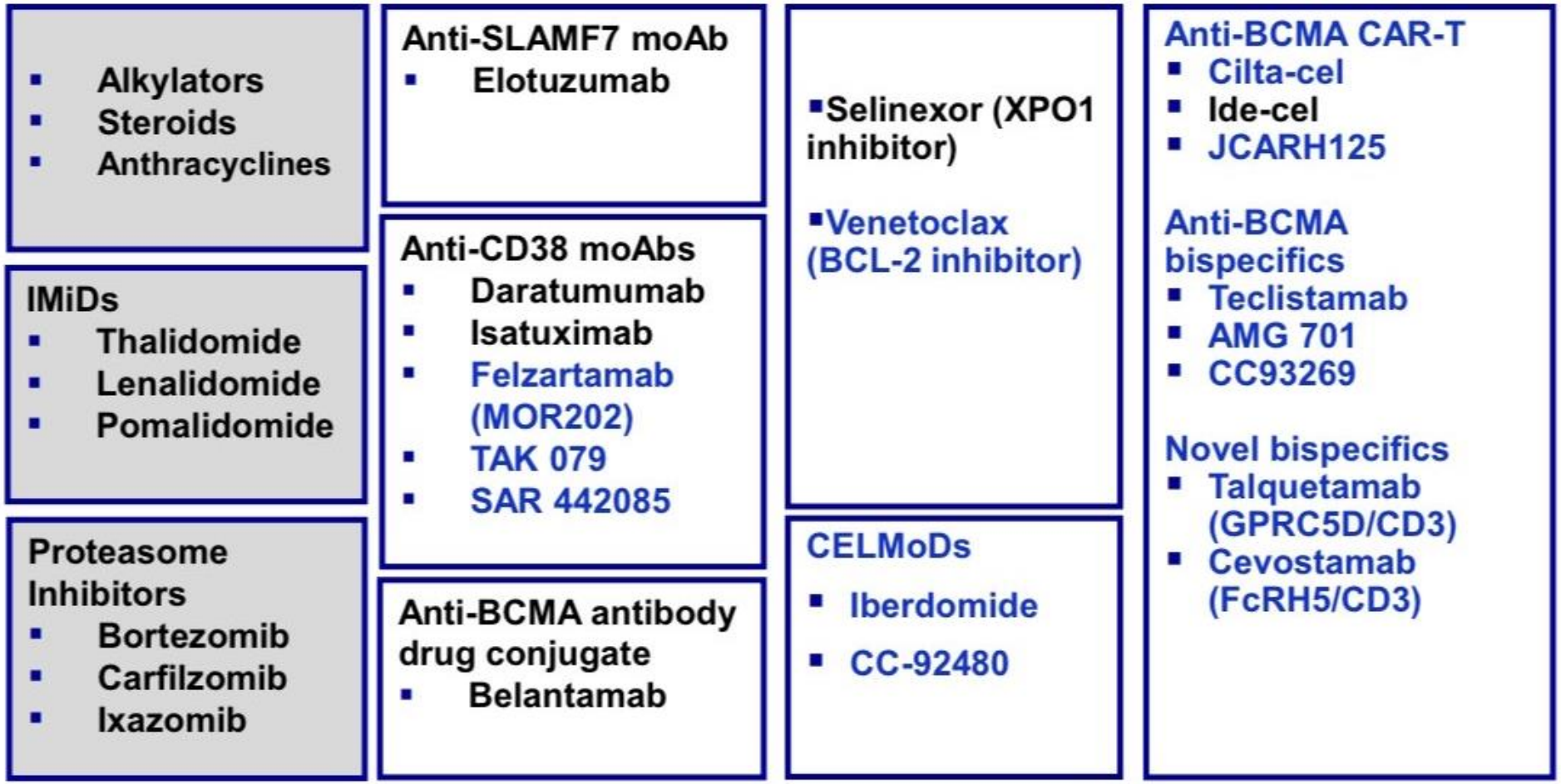
Active Drugs in Multiple Myeloma



moAB: monoclonal antibody

Rajkumar SV. 2022

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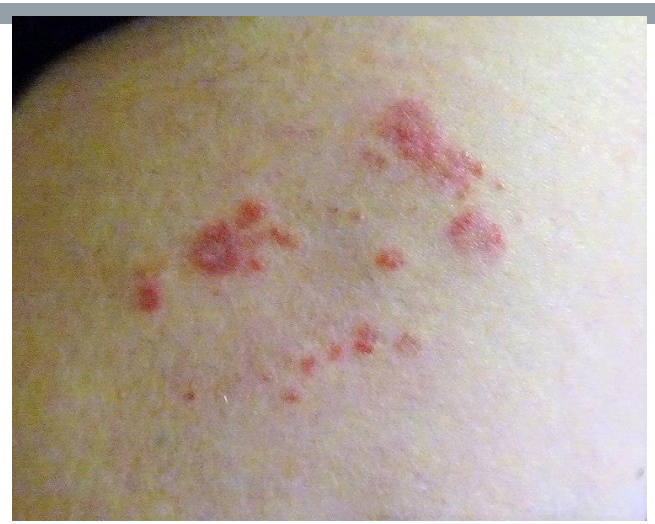
CASE 4 CONTINUES

- 81yo on daratumumab, lenalidomide, dexamethasone.
- Which of the following do you recommend for infectious prophylaxis in this patient?
- A. Bactrim
- B. Pentamidine
- C. Fluconazole
- D. Valacyclovir
- E. Levofloxacin

CASE 4 CONTINUES



- 81yo on daratumumab, lenalidomide, dexamethasone.
- Which of the following do you recommend for infectious prophylaxis in this patient?
- A. Bactrim (the steroids are intermittent, so pneumocystis prophy is not needed)
- B. Pentamidine (the steroids are intermittent, so pneumocystis prophy is not needed
- C. Fluconazole (there is no significant neutropenia expected, and short steroid course)
- D. Valacyclovir (Hypogammaglobulinemia from MM and treatment increase risk of zoster, HSV)
- E. Levofloxacin (no significant neutropenia)

CASE 5

- A 52-year-old man presents with progressive lower extremity edema and dyspnea in addition to lower extremity numbness and paresthesias. He is found to have 3g albumin/24hrs in his urine and an echocardiogram reveals an LVEF of 40% with thickening of the left ventricle. Additional testing identifies an increase in lambda light chain with kappa/lambda ratio of 0.002. M spike is negative.

Laboratory Value	Current	Reference Range
Hemoglobin	11.2 g/dL	12-16 g/dL
Serum		
Calcium (Ca^{2+})	9.6 mg/dL	8.6-10.3 mg/dL
Creatinine	0.8 mg/dL	0.7-1.3 mg/dL
Albumin	2.2 mg/dL	3.0 – 4.3 g/dL

- Bone marrow biopsy reveals 80% lambda-restricted plasma cells.

- Which of the following diagnostic tests do you recommend next for this patient?
  - A. Left heart cardiac catheterization
  - B. Bone marrow congo red stain
  - C. Renal biopsy
  - D. Paraneoplastic antibody panel
  - E. Bone scan

CASE 5

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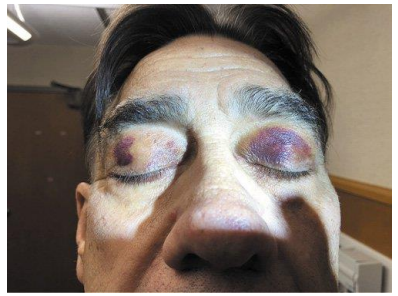
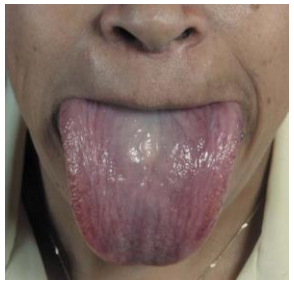
AL AMYLOIDOSIS

- Amyloidosis is caused by extracellular deposition of pathologic insoluble fibrillary protein
  - Most common is AL (due to light chain) but must confirm it is not AA or other with mass spectrometry

Disease	Cause	Affected organs
Light chain amyloidosis	Overproduction of amyloidogenic light chains by clonal plasma cells in the bone marrow	Heart, kidney, nerve, GI, liver, soft tissue
Heavy chain amyloidosis	Overproduction of amyloidogenic heavy chains by clonal plasma cells in the bone marrow	Heart, kidney, liver
ATTRwt amyloidosis	Deposition of transthyretin	Heart, soft tissue, nerve
ATTRm amyloidosis	Mutation in transthyretin	Heart, kidney, soft tissue, nerve
AA amyloidosis	Overproduction of serum amyloid A protein due to chronic inflammation	Kidney, liver, spleen





Vaxman, I and Gertz, M. Acta Haematol 2020;143:304–311

Organ	Clinical signs and symptoms that should raise suspicion of amyloidosis	Typical findings in laboratory testing and imaging	ISA consensus definition for organ involvement
Heart	Shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, jugular venous distention, peripheral edema, arrythmia	ECG: low voltage in limb leads, poor R wave progression in chest leads (pseudoinfarct pattern), rhythm disturbances	NT-pro BNP ≥332 ng/L in the absence of renal failure or atrial fibrillation
		ECHO: Thick walled left and right ventricles, preserved ejection fraction, left and right atrial enlargement, restrictive pattern on Doppler studies	Left ventricular wall thickness ≥12mm
		MRI: Diffuse subendocardial late gadolinium enhancement, thick walled left and right ventricles, preserved ejection fraction, left and right atrial enlargement	
		Elevated cardiac biomarkers	
Kidney	Peripheral edema	Nephrotic syndrome	24 h protein >500 mg/day, predominantly albumin
Nerve	Length-dependent symmetric peripheral neuropathy, autonomic neuropathy (erectile dysfunction, postural hypertension, voiding dysfunction, early satiety, irregular bowel habits)	EMG: often not helpful	
Soft tissue	Macroglossia, hoarseness, obstructive sleep apnea, dysarthria, enlarged salivary glands, dry mouth, arthropathy, jaw claudication, periorbital and other bruising, carpal tunnel syndrome		
GI tract	Irregular bowel habits, early satiety, weight loss, gastroparesis, dysphagia, gastrointestinal bleeding	Low albumin, anemia	
Liver	Hepatomegaly, early satiety, significant unintentional weight loss, bleeding disorders	ALP elevation, PT and PTT prolongation due to low level factor X CT-enlarged liver	Liver span >15 cm in the absence of heart failure, ALP >1.5 XULN
Spleen	Abdominal distension, early satiety, rarely spontaneous splenic rapture	Peripheral blood smear: Howell jolly bodies	
Lung	Shortness of breath, dry cough	CT-interstitial pattern	Interstitial radiographic findings in the absence of pulmonary edema

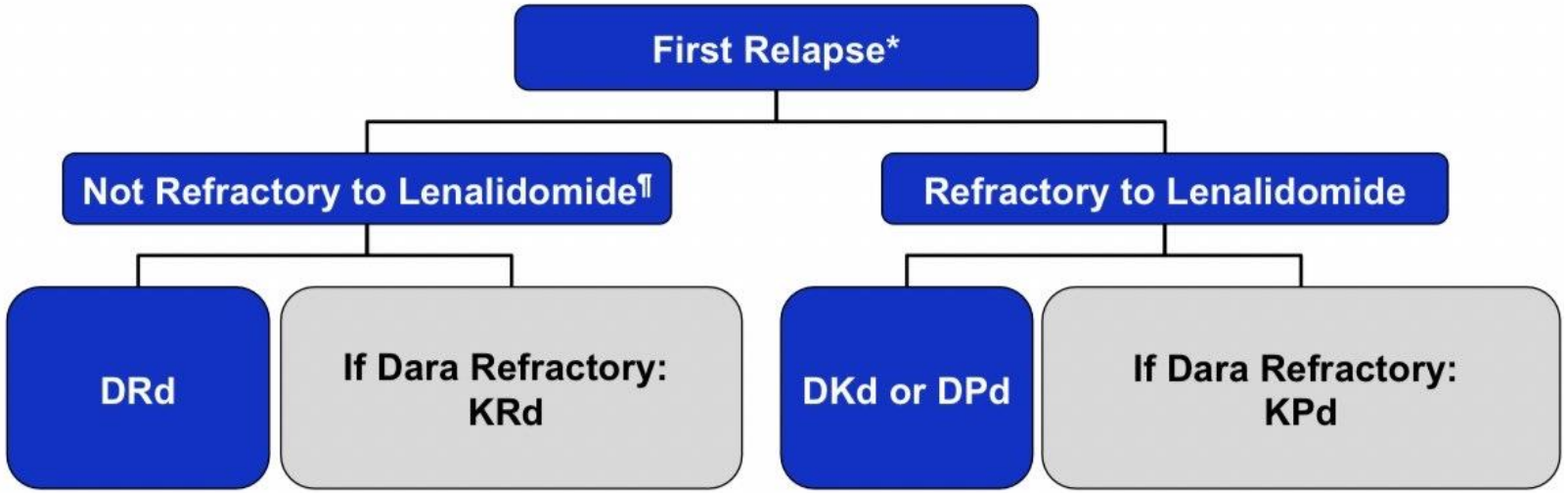
QUESTIONS?

- Matthew.Ulrickson@BannerHealth.com
- @MattUlricksonMD

Drug Development in MM-TCR: *How We Arrived Here*

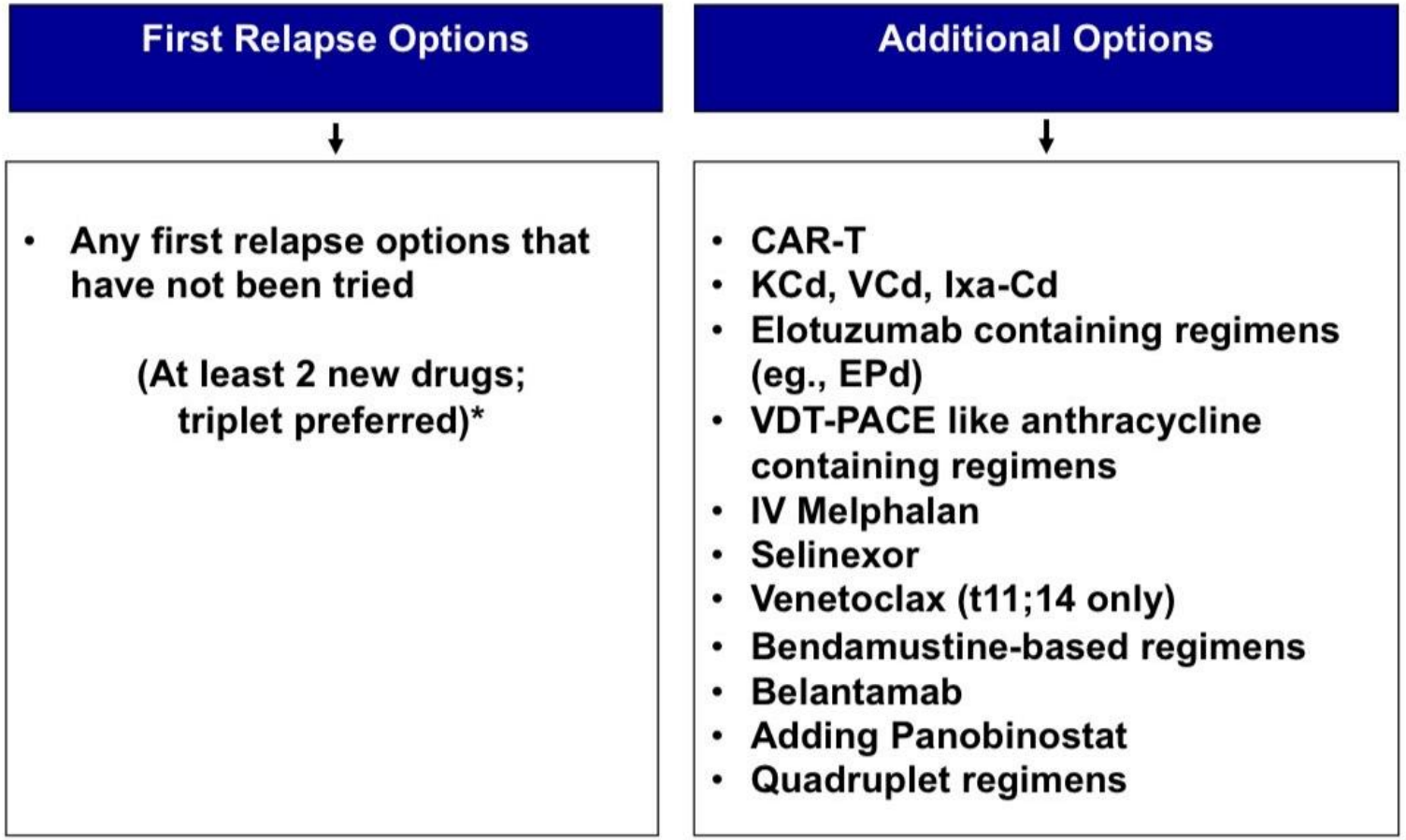
Agent	Setting	Single Agent Response	With Dexa	PFS
Thalidomide[1]	Relapsed MM Post-SCTx	**30%**	**52%**	EFS 20% at 2 yr
Bortezomib[2]	RRMM (6 PLT): steroids 99.5%, thal 83%	**27%**		TTP 6.6 months
Lenalidomide[3]	Prior thal 80%, bort 40%	**25%**	**61%**	4.6 months
Carfilzomib[5]	RRMM (5 PLT): ~100% bort/IMiD	**24%**		3.7 months
Pomalidomide[4]	RRMM (5 PLT): 100% bort/len	**18%**	**33%**	2.7 months
Isa/Dara[6,7]	RRMM (5 PLT): 100% bort/IMiD	**24-29%**		3.7 months
Belantamab[8,9]	Phase 1 : no Dara (5 PLT:100%-PI/IMiD)	**60%**		12 months
	Phase 2: Dara-required (7 PLT: 100% Dara/PI/IMiD)	**31%**		2.9 months

Myeloma 2022: First Relapse

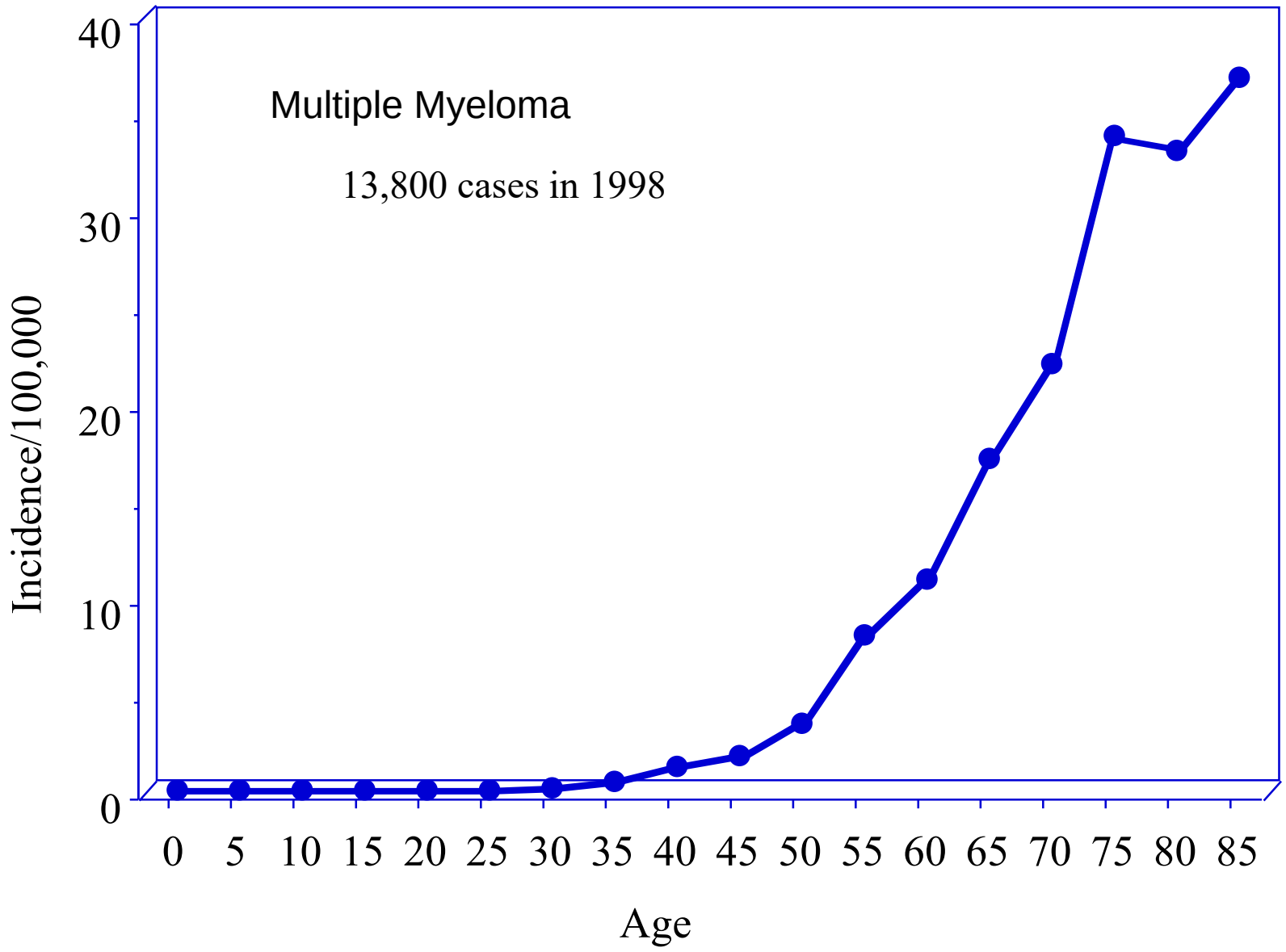


*Consider salvage auto transplant in eligible patients
¶Relapse occurring while off all therapy, or while on small doses of single-agent lenalidomide, or while on bortezomib maintenance

Myeloma 2022: Second or Higher Relapse

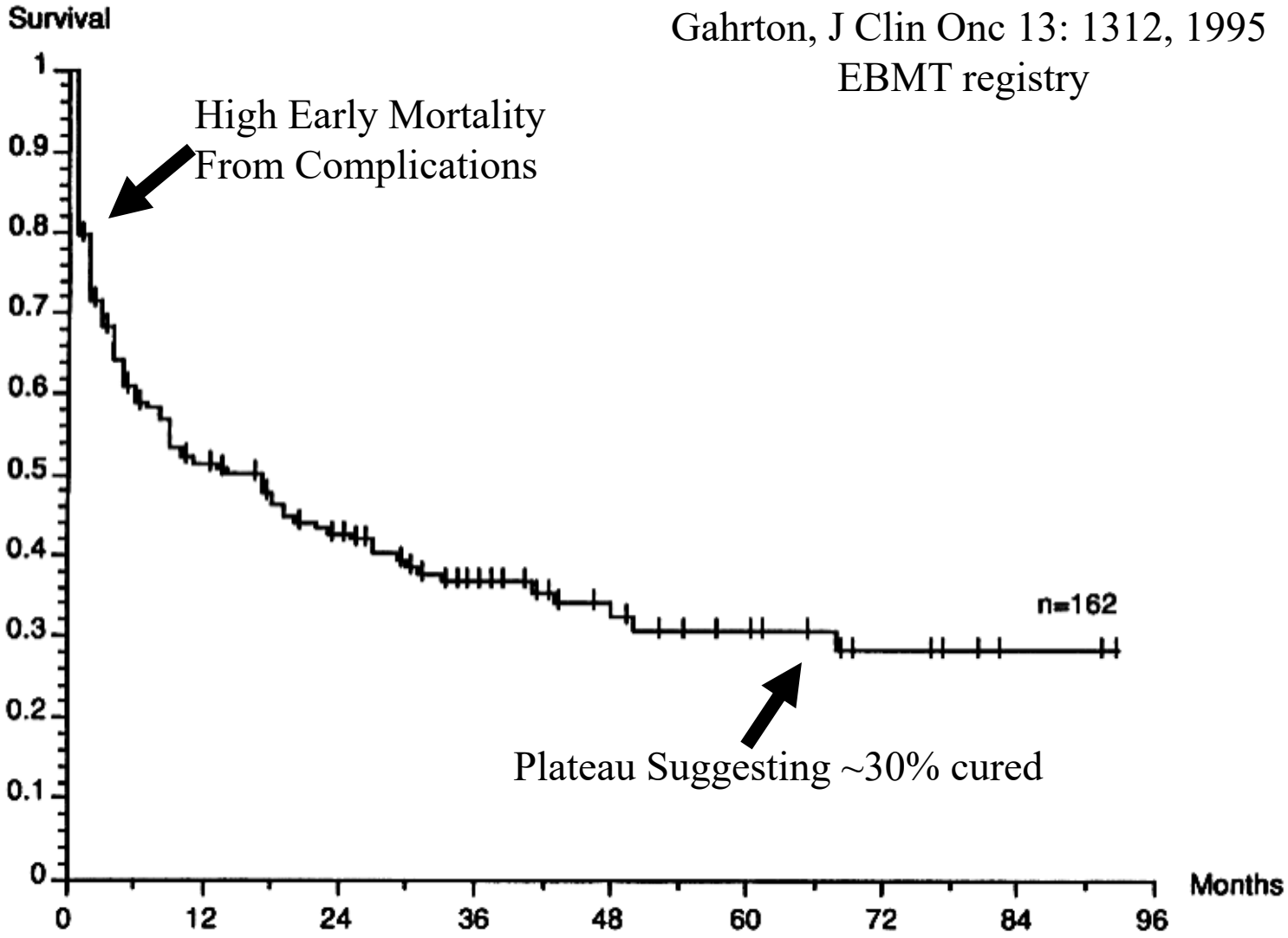


*Consider ixazomib instead of bortezomib or carfilzomib if an all oral regimen is needed.

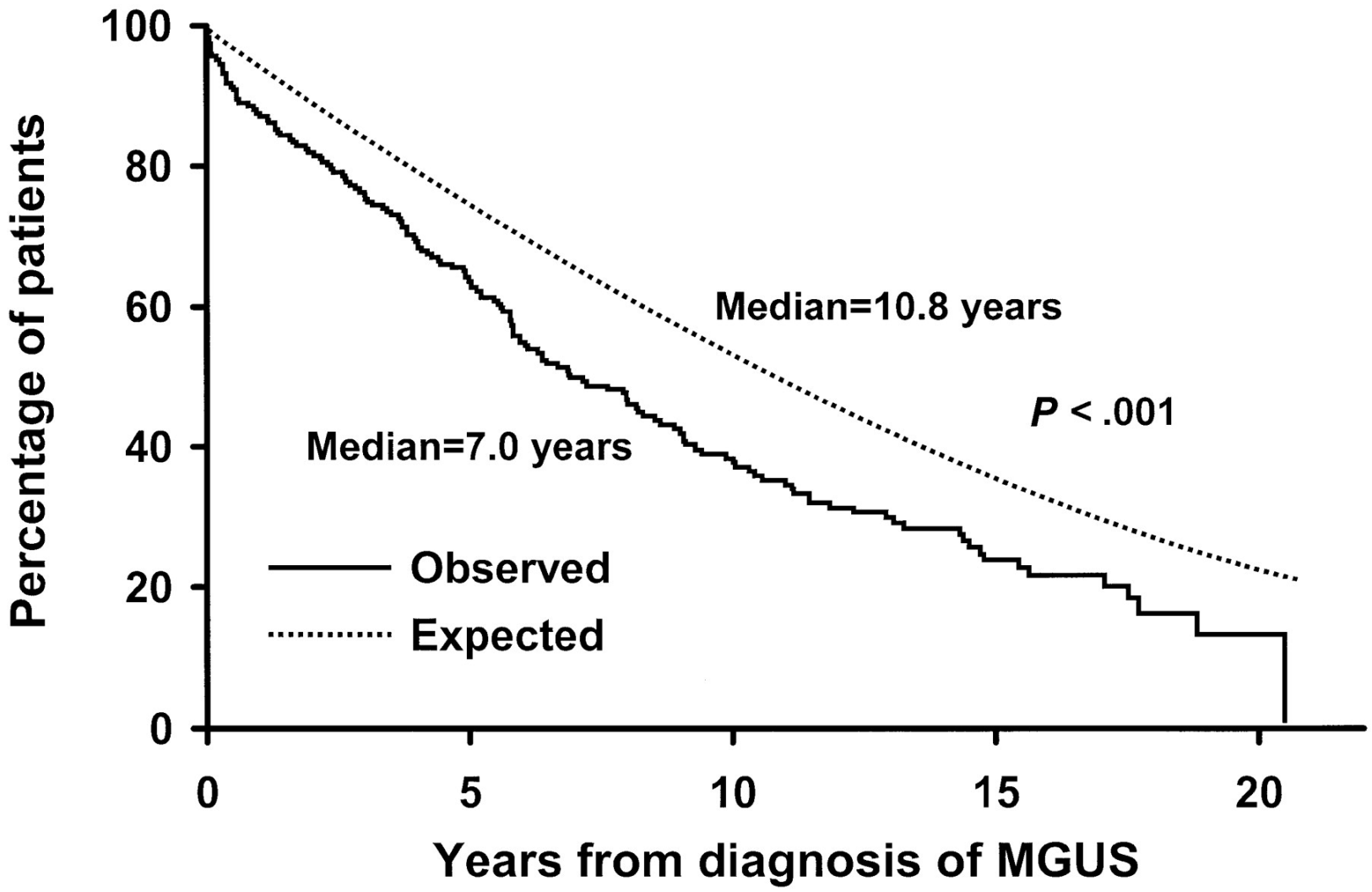

Multiple Myeloma
13,800 cases in 1998
Incidence/100,000
40
30
20
10
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85
Age

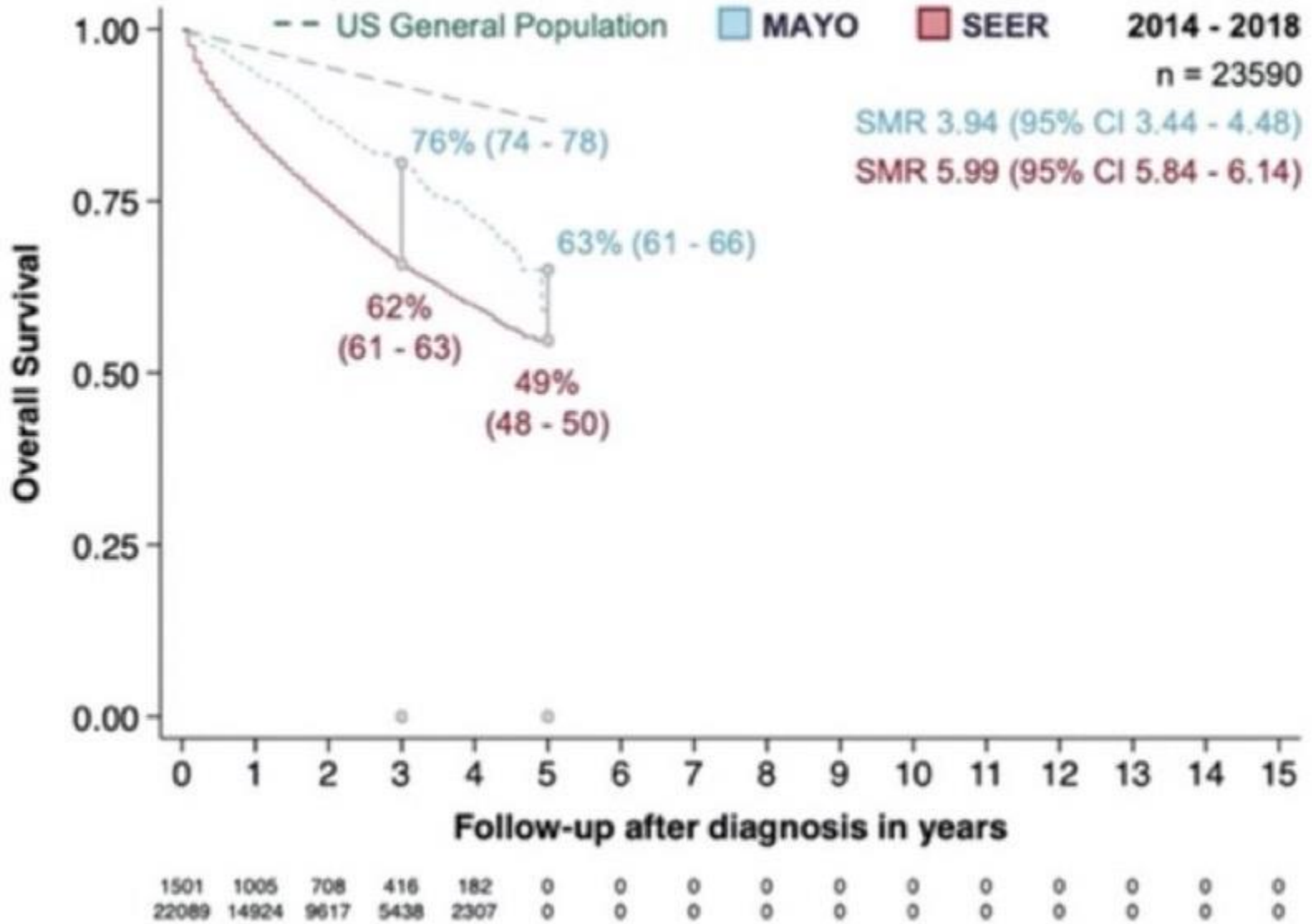
MYELOMA: SURVIVAL AFTER ALLOGENEIC BMT

Gahrton, J Clin Onc 13: 1312, 1995
EBMT registry



IgM MGUS: Survival




US General Population
MAYO
SEER
2014 - 2018
n = 23590
SMR 3.94 (95% CI 3.44 - 4.48)
SMR 5.99 (95% CI 5.84 - 6.14)
76% (74 - 78)
63% (61 - 66)
62%
(61 - 63)
49%
(48 - 50)
Overall Survival
1.00
0.75
0.50
0.25
0.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Follow-up after diagnosis in years
1501 1005 708 416 182 0 0 0 0 0 0 0 0 0 0 0
22089 14924 9617 5438 2307 0 0 0 0 0 0 0 0 0 0 0

BISPHOSPHONATE USE

- ASCO guidelines for bisphosphonates in MM
  - Limit duration to 2 years in responsive/stable disease
  - Restart bisphosphonate when new skeletal-related event
  - Dental evaluation recommended before starting agent

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Durie-Salmon Staging System for MM

Stage	Criteria	Myeloma Cell Mass ($\times 10^{12}$ cells/m^2)
I	All of the following: Hemoglobin >10 g/dL Serum calcium level <10.5 mg/dL (normal) Normal bone or solitary plasmacytoma on x-ray Low M-component production rate: IgG <5 g/dL; IgA <3 g/dL Bence Jones protein <4 g/24 hr	<0.6 (low)
II	Not fitting stage I or III	0.6–12 (intermediate)
III	One or more of the following: Hemoglobin <8.5 g/dL Serum calcium level >12 mg/dL Advanced lytic bone lesions on x-ray High M-component production rate: IgG >7 g/dL; IgA >5 g/dL Bence Jones protein >12 g/24 hr	>1.2 (high)

Subclassification	Criteria
A	Normal renal function (serum creatinine level <2.0 mg/dL)
B	Abnormal renal function (serum creatinine level ≥2.0 mg/dL)

Durie BG, Salmon SE. *Cancer*. 1975;36:842; Multiple Myeloma Research Foundation. Available at: www.multiplemyeloma.org

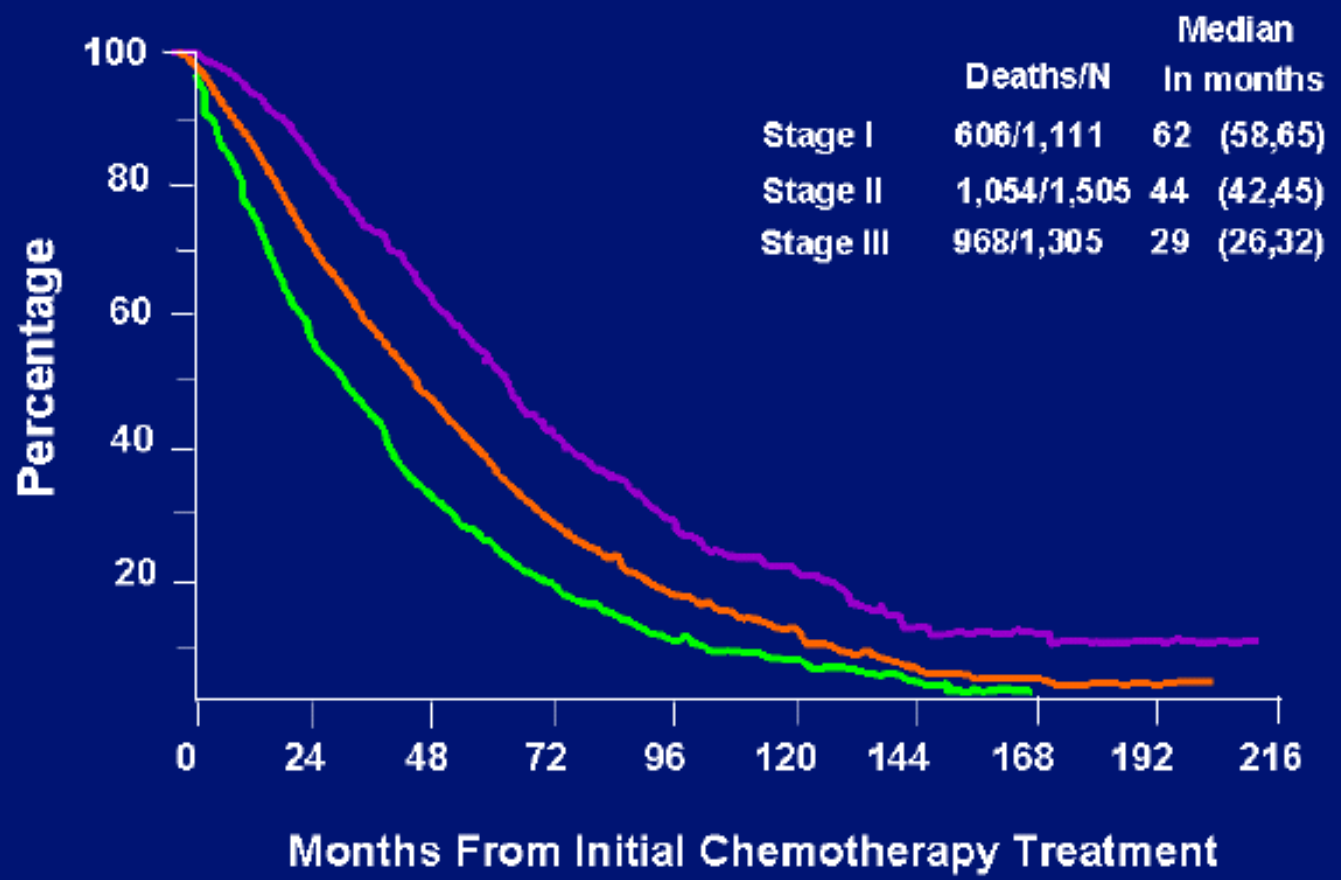
International Staging System for MM

Stage	Criteria	Median Survival
I	Serum β_2M <3.5 mg/L Serum albumin ≥3.5 g/dL	62 mo
II	Serum β_2M <3.5 mg/L Serum albumin <3.5 g/dL **OR** Serum β_2M 3.5 to <5.5 mg/L*	44 mo
III	Serum β_2M ≥5.5 mg/L	29 mo

*Irrespective of serum albumin level

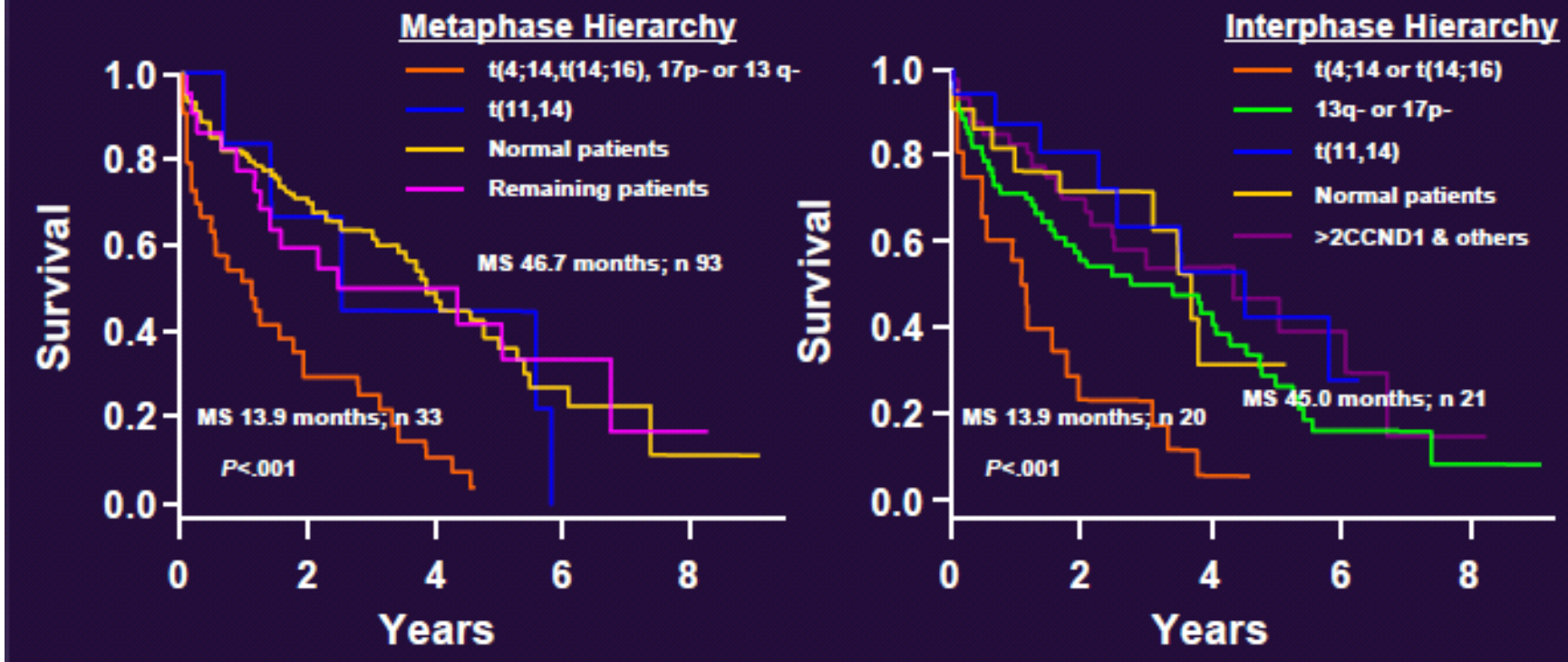
Greipp PR et al. *J Clin Oncol*. 2005;23:3412

ISS: Survival



Greipp PR et al. *J Clin Oncol*. 2005;23:3412

Prognostic Significance of Genetic Anomalies in MM by FISH



- Patients with the t(4;14),t(14;16) translocation, deletions of 17p, or chromosome 13 abnormalities had statistically significant lowered survival

FISH=flouresence in situ hybridization.

Dewald GW et al. *Blood*. 2005;106:3553-3558.

THREE-DRUG REGIMENS (2)

Regimen	Dosing	Schedule
CyBorD	Cyclophosphamide 300mg/m2 PO d1,8,15,22 Bortezomib 1.3mg/m2 IV/SC d1,8,15,22 Dexamethasone 40mg PO d1,8,15,22	Every 4 weeks
VRd	Bortezomib 1.3mg/m2 IV/SC d1,8,15 Lenalidomide 25mg PO d1-14 Dexamethasone 20mg PO d1,2,8,9,15,16,22,23	Every 3 weeks
VAD	Vincristine 0.4mg d1-4 Doxorubicin 9 mg/m2 iv d1-4 Dexamethasone 40mg PO d1-4, 9-12, 17-20	Every 4 weeks Barlogie et al. NEJM 1984. 310:1353 ORR 75% Median time to response 0.9m

RESPONSE RATES

Trial	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	Progression-free survival (median in years)	3-year overall survival rate (%)[a]	Overall survival (median in years)	*P* value for overall survival
Rajkumar et al. [57]	RD	223	81	50	19.1	75	NR	
	Rd	222	70	40	25.3	74	NR	0.47
Harousseau et al. [71]	VAD	242	63	15	30	77	NR	
	VD	240	79	38	36	81	NR	0.46
Cavo et al.64, [72]	TD	238	80	31	NR	N/A	N/A	
	VTD	236	93	62	NR	N/A	N/A	
Moreau et al. [73]	VD	99	81	35	N/A	N/A	N/A	
	VTD	100	90	51	N/A	N/A	N/A	
Facon et al. [59]	MP	196	35	7	17.8	48	33.2	
	Mel 100	126	65	43	19.4	52	38.3	
	MPT	125	76	47	27.5	66	51.6	<0.001
Hulin et al. [60]	MP + Placebo	116	31	7	18.5	40	29.1	
	MPT	113	62	21	24.1	55	44	0.028
Wijermans et al. [74]	MP	168	45	10	9	43	31	
	MPT	165	66	27	13	55	40	0.05
Palumbo et al. [75]	MP	164	48	11	14.5	65	47.6	
	MPT	167	69	29	21.8	65	45	0.79
Waage et al. [76]	MP + Placebo	175	33	7	14	43	32	
	MPT	162	34	23	15	43	29	0.16
San Miguel et al. [61,77][b]	MP	331	35	8	16.6	54	43	
	VMP	337	71	41	24	69	NR	<0.001

Rajkumar. Am J Heme 2011. 86:57

PROTEASOME INHIBITORS

- Bortezomib
- Carfilzomib
  - Neuropathy
  - Herpes virus reactivation

BORTEZOMIB: WEEKLY VS TWICE-WEEKLY

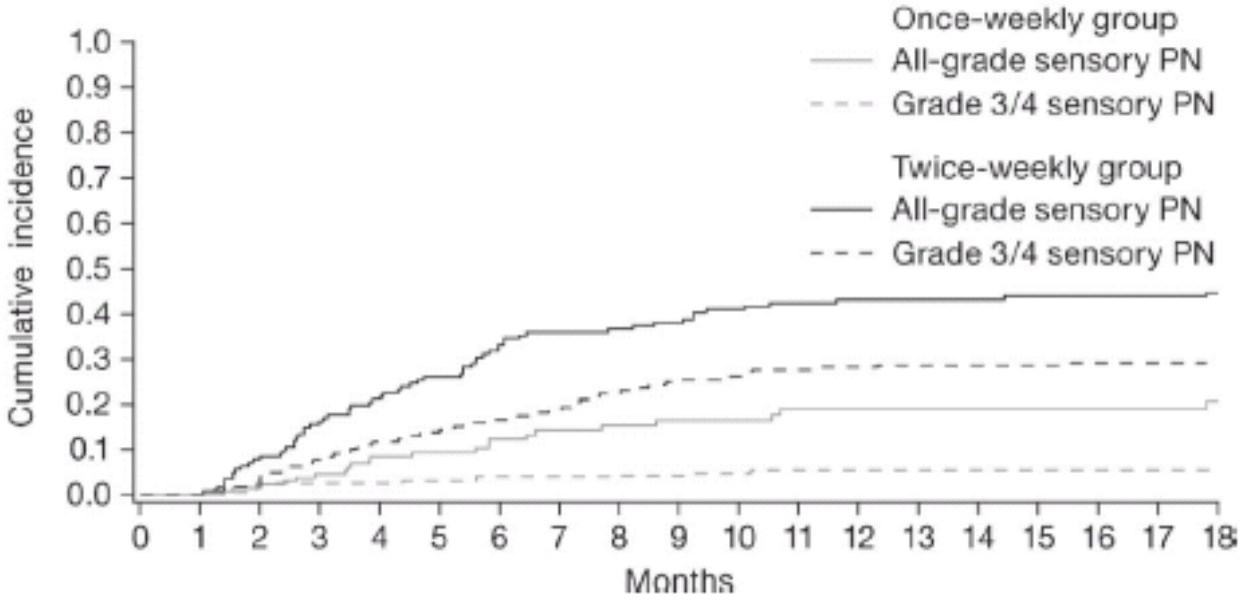


Figure 2. Cumulative incidence of sensory PN, accounting for competing events (death and any other PN type) in patients who received once-weekly or twice-weekly bortezomib. The cumulative incidence of PN rate increased over time, reaching a plateau after 12 months of therapy.

Bringhen et al. Blood 2010. 116:4745.

POEMS

- Polyneuropathy
- Monoclonal plasma cell disorder
- 1 of 3 major criteria
  - Sclerotic bone lesions
  - Castleman's disease
  - Elevated VEGF
- 1 of 6 minor criteria
  - Organomegaly (spleen/liver/LAD)
  - Volume overload (edema/ascites/effusion)
  - Endocrinopathy (thyroid/adrenal/pituitary/gonadal/parathyroid)
  - Skin changes
  - Papilledema
  - Thrombocytosis/polycythemia

BISPHOSPHONATES

- Hypocalcemia in setting of low vitamin D
- Renal Insufficiency
- Osteonecrosis of the jaw (ONJ)
  - myeloma patients: 1-5% incidence
  - Unhealed lesion persisting for >8 weeks without prior XRT or disease in the area
  - Dental procedures precede about ½ of ONJ cases

ONJ

- Supportive care with chlorhexidine rinse, antibiotics as needed, careful sequestrectomy
- Avoid bone curettage and surgical debridement
  - Most cases worsen after surgery

BISPHOSPHONATE USE

- ASCO guidelines for bisphosphonates in MM
  - Limit duration to 2 years in responsive/stable disease
  - Then restart bisphosphonate when new skeletal-related event
  - Dental evaluation before starting agent

HISTORICAL PERSPECTIVE

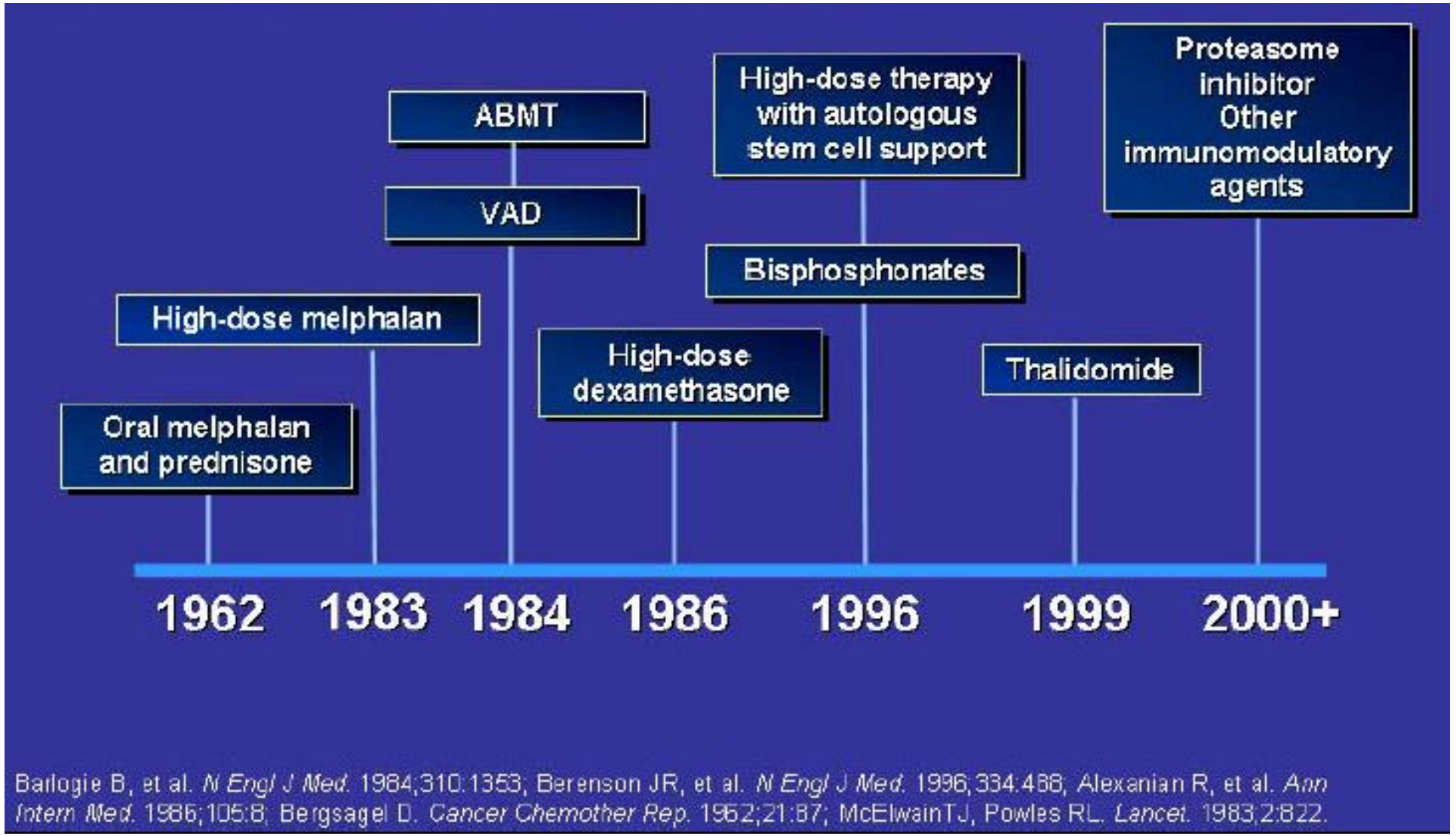


Table 3. Treatment of Complications in Multiple Myeloma.

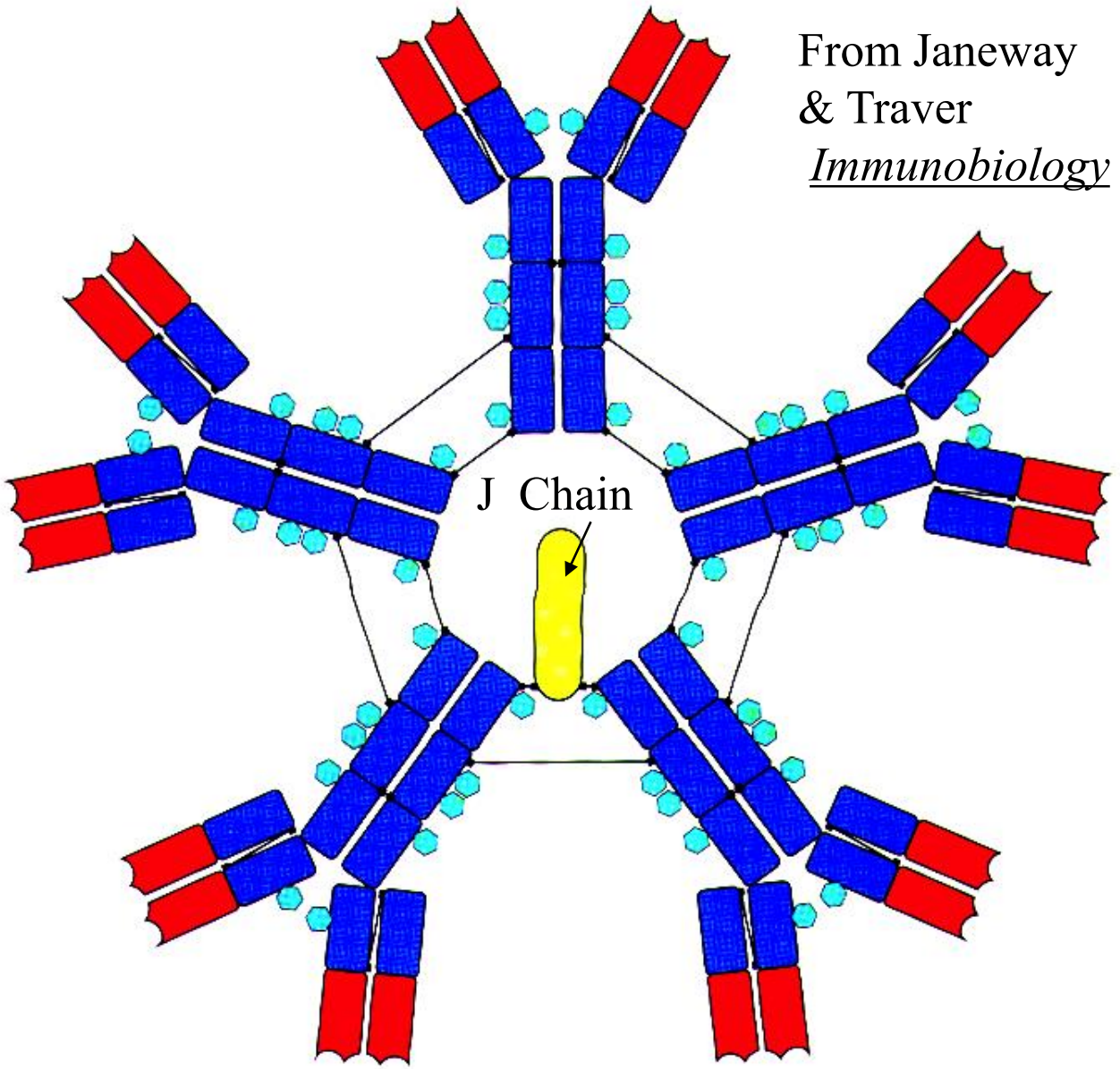
Complication	Therapeutic Options
Myeloma bone disease	Pamidronate or zoledronic acid in patients with documented bone disease Encouragement of activity to prevent osteopenia and deep-vein thrombosis Pain control with narcotic analgesics, if needed; avoidance of nonsteroidal antiinflammatory agents Radiation to treat painful bony lesions refractory to pain medication or cord compression Surgical intervention to prevent or treat pathologic fractures Vertebroplasty or kyphoplasty for selected vertebral lesions, to reduce pain and improve height
Anemia	Treatment of reversible causes such as deficiencies of iron, B_{12}, or folate Erythropoietin for symptomatic anemia during chemotherapy Transfusions as needed
Infections	Vaccination against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and influenza Consideration of prophylactic broad-spectrum antibiotic therapy when corticosteroids are used Intravenous immune globulin for recurrent serious infections associated with hypogammaglobulinemia Consideration of prophylaxis against *Pneumocystis carinii* when prolonged corticosteroid therapy is used; avoidance of trimethoprim–sulfamethoxazole when thalidomide is used
Hypercalcemia	Intravenous fluids and corticosteroids Bisphosphonates when hypercalcemia is severe or unresponsive to hydration and corticosteroids
Renal failure	Correction of reversible causes such as dehydration, hypercalcemia, and hyperuricemia Chemotherapy (e.g., vincristine, doxorubicin, and dexamethasone; dexamethasone alone; or thalidomide–dexamethasone) for rapid control of disease Alkaline diuresis for acute renal failure due to cast nephropathy; avoid alkalinization in patients with hypercalcemia Trial of plasma exchange in acute evolving renal failure
Hyperviscosity syndrome	Plasma exchange for symptomatic patients (serum viscosity does not correlate well with symptoms)

Kyle, NEJM 2004

WALDENSTROM'S MACROGLOBULINEMIA

- 1. Low Grade B Cell Lymphoplasmacytic Lymphoma
- 2. IgM Monoclonal Gammopathy (usually >2.5 gm/dL)

Pentameric IgM



WALDENSTROM'S MACROGLOBULINEMIA

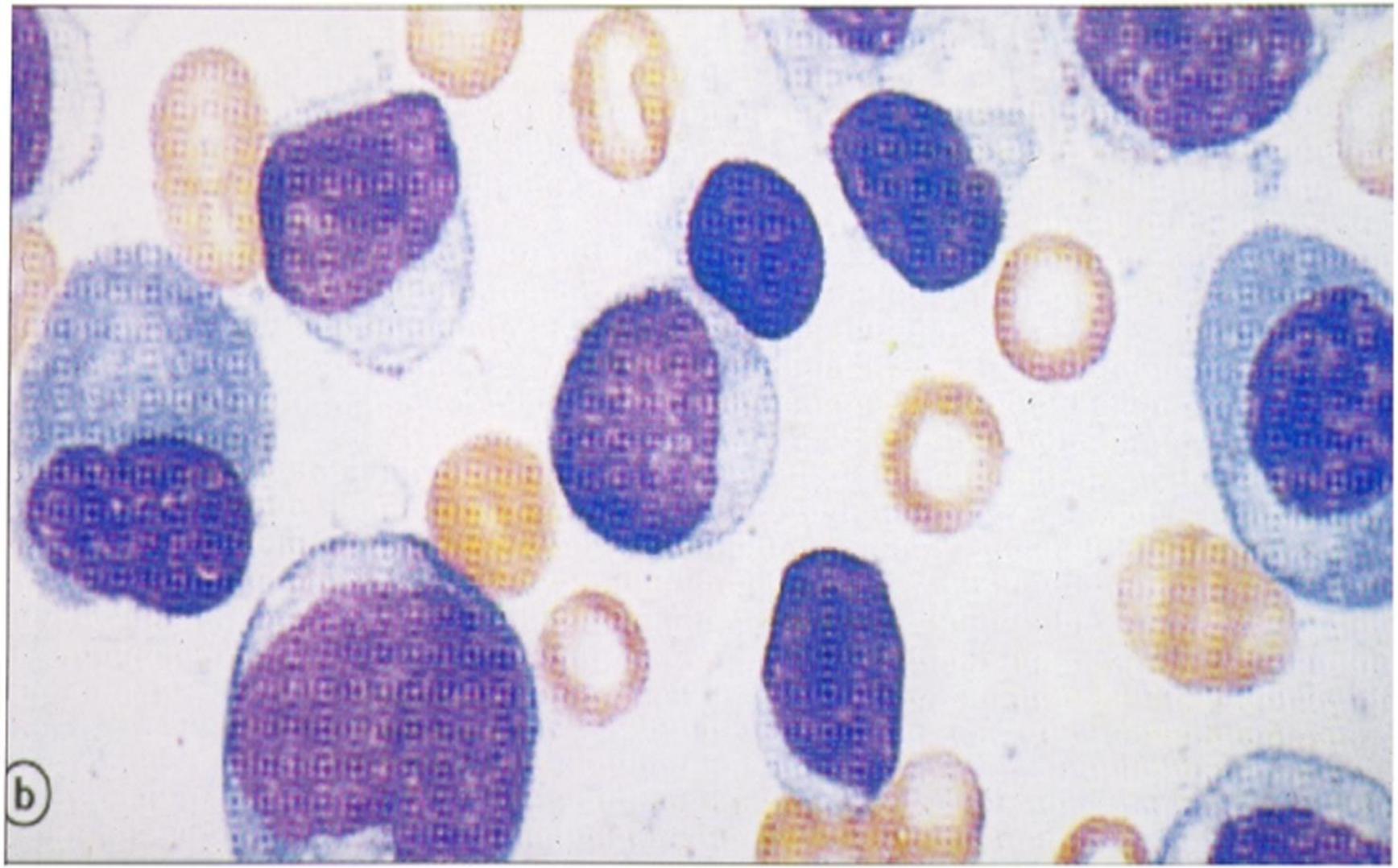
- 1. Low Grade B Cell Lymphoplasmacytic Lymphoma

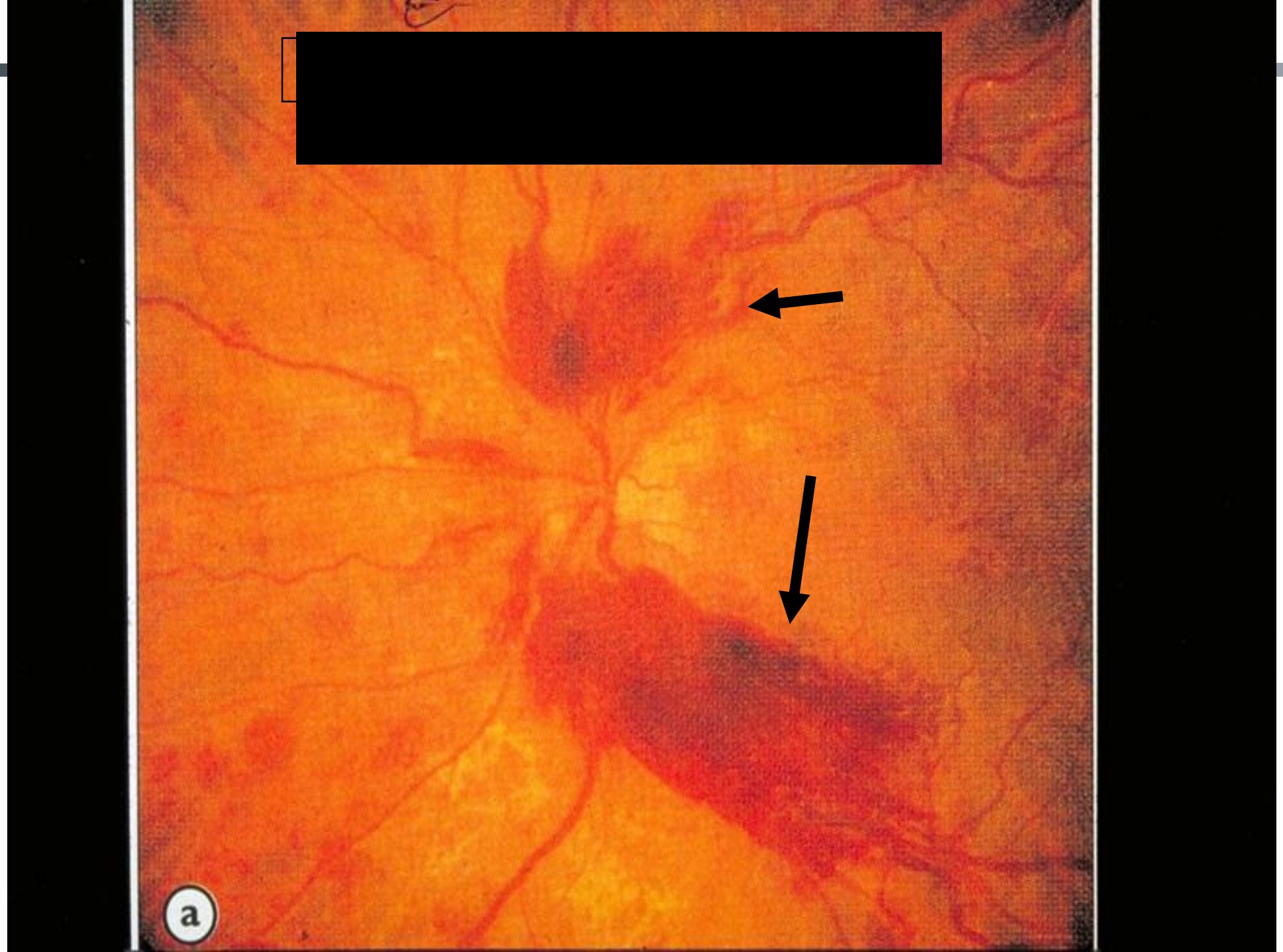
- 2. IgM Monoclonal Gammopathy (usually >2.5 gm/dL)

- 3. Classic Triad for "Hyperviscosity Syndrome"
  - **a. Bleeding (e.g. Epistaxis, Ecchymoses)**
  - **b. Visual Changes (blurred vision, segmentation of retinal vessels)**
  - **c. Neurologic (Headache, confusion, dizziness)**

- 4. Other Features
  - a. Fatigue in 85%
  - b. Hypervolemia: CHF, venous distension
  - c. Lymphadenopathy ± splenomegaly
  - d. Bone marrow infiltrated with tumor cells

Waldenstrom's Macroglobulinemia: Lymphoplamacytic cells

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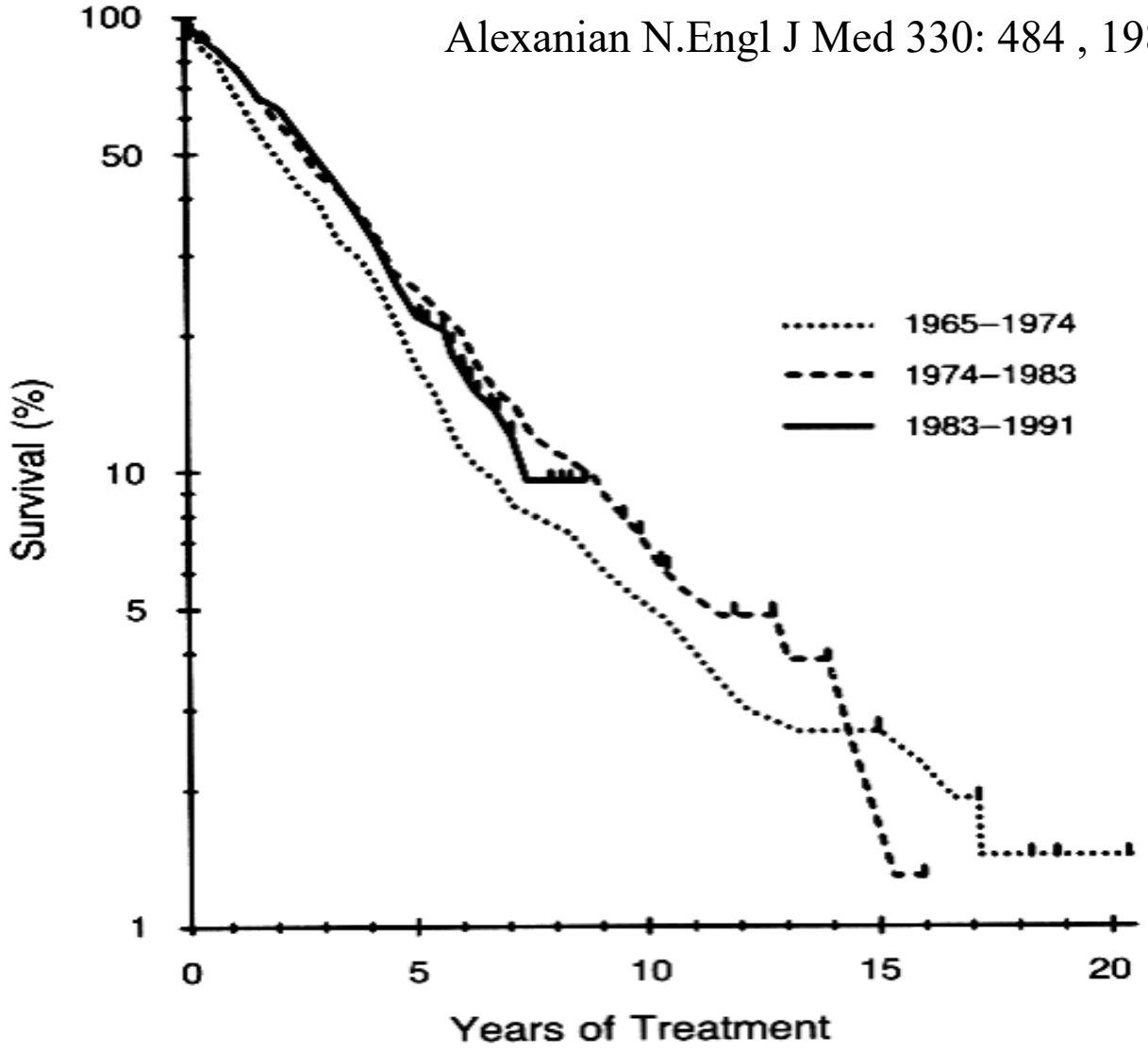
MYELOMA: SURVIVAL WITH STANDARD CHEMOTHERAPY

Alexanian N.Engl J Med 330: 484 , 1984



WALDENSTROM'S: THERAPY

- 1. Chlorambucil ± prednisone
- 2. Fludarabine
3. Rituximab
4. Bortezomib
- 5. Plasmapheresis if hyperviscosity symptoms
- (relative serum viscosity usually > 4)
  - *Median Survival: 60 Months*

CASE 2 AND 3

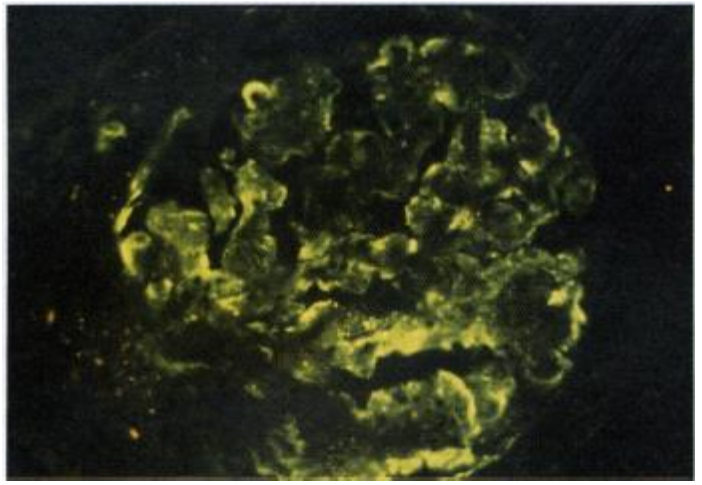
- No acute findings and Cr 2.5
  - 55yo with CKD
  - monoclonal IgM kappa

- No acute findings and Cr 2.5
  - 70yo with CKD
  - monoclonal IgG kappa

MONOCLONAL SPIKE

- 55yo with CKD
- monoclonal IgM kappa
- Renal biopsy with 3+ IgM and 4+ kappa, revealing MPGN

- 70yo with CKD
- monoclonal IgG kappa



Johnson. NEJM 1993. 328:465

MONOCLONAL SPIKE

- RM
  - 55yo with CKD
  - monoclonal IgM kappa on SPEP
  - Renal biopsy with 3+ IgM and 4+ kappa, revealing MPGN
  - + Hepatitis C
  - + Cryoglobulins
- PW
  - 70yo with CKD
  - monoclonal IgG kappa
  - Hepatitis negative
  - MGUS related MPGN (MGRS)

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

- Sometimes lower quantities of paraprotein can deposit in the renal tubules and contribute to renal injury.
- Renal biopsy is necessary to confirm in the absence of a diagnosis of myeloma

Myeloma Cells in the Marrow